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The Present Status of Treament of Subacute Bacterial Endocarditis

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Some considerations concerning the fundamental pathology of bacterial endocarditis which have a bearing on treatment are discussed. In using antibiotics the importance of time-dose relationships is emphasized. It is pointed out that tests for strain sensitivity give a useful clue to the total daily dosage but that regardless of this, treatment must be carried out over a period of at least a month in order to achieve permanent bacteriologic cures. The difficulties and complications of treatment are discussed. Special methods for the treatment of highly resistant strains and the results with some of the newer antibiotics are outlined.

I WANT to say first of all how very much I appreciate the honor of being invited to give the Lewis A. Conner Lecture before the members of the American Heart Association. As an internist whose practice is in no sense confined to cardiology I hesitated to accept, but then I took courage from the realization that Dr. Conner himself was, after all, primarily a general doctor who, only after years of practice, claimed a special interest in problems of the circulation. Furthermore, the title suggested by your Chairman was too tempting to resist when one realizes that the new treatment of bacterial endocarditis is, barring insulin, probably the greatest therapeutic triumph of the century in internal medicine.

We were fortunate, as long ago as 1943, in being asked to participate in the bacterial endocarditis program of the Committee on Medical Research.[1] Six years of experience have modified some of our original views, but more or less definite policies as to procedure have now become crystallized, and these we wish to bring before you today. We shall touch especially on the use of newer preparations, singly and in combination, on routes of administration of antibiotics, and on the importance of sensitivity tests in determining time-dose relationships. It is perhaps only natural that emphasis be placed on the work of our own group.

It would be superfluous to review to this audience the background, clinical features, and bacteriologic findings of infectious endocarditis; they are familiar to all.[2, 3] It may be recalled, however, that prior to the introduction of penicillin most clinicians, even those of wide experience, could not recall instances of actual recovery from proved bacterial endocarditis.[4] At best, the measures then in vogue, such as sulfonamides and anticoagulants, were a feeble crutch to lean on and the hazards of therapy almost outweighed the occasional cure which was claimed.[5] One felt that another such vic-

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tory and like Pyrrhus we would be undone. Now, although all concede the brilliant results of penicillin therapy there are somewhat divergent views as to just how recovery is effected, and this makes it necessary to outline a few fundamental concepts of *Streptococcus viridans* endocarditis.

The Nature of Subacute Bacterial Endocarditis

Lenhartz[6] in Germany, Horder[7] in England, and Osler,[8] Libman,[9] and others in this country early noted the slow and relentless character of the disease. Schottmuller's[10] designation of "endocarditis lenta" pictures well the insidious onset and vague course so often observed. We recall a patient who enjoyed his horseback ride each morning but went to bed with fever every afternoon for months before he was forced to discontinue his activities. A medical student, informed of the diagnosis in her freshman year, went on with her studies for two years with great assiduity. The stormy course occasionally pursued by the disease only emphasizes the usual insidious progress.

Now, when one turns to the character of the lesions some light seems to be thrown on the clinical events. Harbitz[11] years ago, and Libman[12] and others noted that in the verrucous excrescences on valves or endocardium there is often a distinct tendency to fibrosis, scarring and calcification which takes place especially in the older portions of the lesion. In other words the thrombotic vegetative process may spread slowly, fresh and active at the periphery, while healing of a sort takes place in the older or central part. Modern pathologists[13] and clinicians[14] also accept this interpretation. One has, therefor , the paradox of a disease which in the clinicians' hands, if untreated, is always fatal but which to the pathologist shows definite signs of arrest. No less important is the distribution of the cocci in the usual form of *S. viridans* endocarditis. While they are readily stained in the superficial parts of the vegetations, masses of organisms may also be seen trapped and encased in the deeper fibrotic and perhaps even calcified reaches of the lesion, or buried beneath a mass of platelets and fibrin.

These considerations have, we believe, an important bearing on the rationale of treatment with antibiotics. One needs first of all an agent which will prevent the relentless peripheral spread of the lesion. If this can be arrested, then there is time for a long attack on the cocci buried in the older vegetations so that the natural tendency to organization and healing may take effect. In actual practice it is indeed very hard to say to what extent healing is due to direct antibiotic action and how much nature contributes. At any rate it must be quite clear that the essence of the treatment is time. No agent, no matter how great its bactericidal effect, can be expected to dislodge cocci from the depths of vegetations in just a few days[15,16]; the agent must be present over a long period to aid and abet the natural healing process and to nip off any organisms which stray to accessible surfaces. Otherwise, viable bacteria dormant in the vegetations may again light up an active and progressive process. That this position is sound was shown early by the observations of Christie[17] on time-dose relationships. He demonstrated that a large amount of penicillin per day for a short time was followed by prompt relapse when the same total dose spread over a longer time effected cure. The common experience during the early days of penicillin of recrudescence in too briefly treated cases confirms these purposeful observations.

Time-Dose Relationships

Assuming that an appropriate daily dose of an antibiotic has been selected, over how many weeks should uninterrupted treatment be continued? In our early cases we arbitrarily treated for 60 days[1] and as it happened, this turned out to be a fully adequate period. It is not likely that anything would often be gained by more prolonged therapy. Even so, in a patient who died of cardiac failure four months after "cure" of her bacterial endocarditis by penicillin, masses of cocci could still be seen in the depths of the scarred mitral valve. These lesions are beautifully pictured in the paper by Carnes and Tinsley.[18] Recently we have wondered whether 60 days may not be too long and Rantz and his associates[19] in our clinic have convinced

themselves that 30 days of continuous treatment, provided the daily dose is adequate, yields equally good results. Periods of therapy short of this must, however, be definitely classed as bad practice.

What, then, is the adequate daily dose and how should it be administered? To answer this question intelligently it is essential to isolate and identify the causal organism and to test its sensitivity to the available antibiotics. Many strains of *S. viridans* can be grown only with considerable difficulty. Repeated blood cultures at intervals of a few days, a dozen if necessary, should be made using solid and liquid media kept under both anaerobic and aerobic conditions. In one of our patients a single colony on the fourteenth culture confirmed the clinical diagnosis. We have summarized elsewhere the reasons why failure to recover bacteria in ordinary cultures does not exclude the presence of living organisms in the vegetations or in the blood stream.[20] Even arterial blood gives only slightly higher counts than blood from antecubital veins according to the thorough studies of Beeson and his colleagues.[21] So that occasionally a patient with adequate clinical evidence must be treated even though there is no bacteriologic confirmation. In such cases, or if strain sensitivity has not been tested,* it seems advisable to err on the side of heavy penicillin dosage—4 to 12 million units daily.

In the early days of penicillin therapy the question was often raised as to whether it was necessary to keep up a high blood level of the antibiotic around the clock. Continuous intravenous drip was used at first in the hope of maintaining such a level. Subsequently it appeared that an injection every three hours might be equally effective and that continuous infusions of penicillin were not necessary. If the time between injections is lengthened, however, blood levels fall to an insignificant point and actual practice shows that results may be less secure regardless of theoretic considerations. This is well illustrated in the case reported below under reinfection. One hundred thousand units given every six hours failed to extirpate the infection, but 50,000 units every three hours sterilized the blood stream. Today, of course, the question of the number of daily doses is to some extent a dead letter since the slowly absorbed penicillin now in general use maintains desired blood levels even if the total 24 hour dose is given in only one or two injections.

* In our clinic sensitivity tests have been carried out under the supervision of Dr. L. A. Rantz by a method in which the organism is planted on blood agar plates containing various concentrations of the antibiotic.

Importance of Sensitivity Tests

Not all have agreed that sensitivity tested in vitro gives the correct answer to clinical dosage but an actual exploration of the subject has convinced us[22] as well as others[23] that such testing is of the greatest practical value. In the early work patients whose strains of *S. viridans* were inhibited by 0.05 unit or less of penicillin per cc. of culture medium were uniformly cured (and never yielded another positive blood culture) by daily doses of only 200,000 to 320,000 units of penicillin, but today we would usually give a larger amount. Patients with strains requiring 0.1 unit for test-tube inhibition were invariably and securely cured by doses of 400,000 units daily. When test tube inhibition required larger amounts (0.2 to 0.4 unit per cc. or more) such standard therapy failed in every case and much larger doses of penicillin were necessary. If the strain was even more resistant, we learned that very large doses (5 million to 20 million units daily) might be required, and in such cases the virtues of other antibiotics or combinations of several, should be explored.

An important question is whether subcurative doses of penicillin may lead to increased resistance on the part of *S. viridans*.[24] We have seen 2 cases in which such increased resistance occurred. In one the inhibiting dose rose from 0.2 to 1 unit per cc., in the other from 0.4 to 3.2 units per cc. In both, sensitivity increased when penicillin was temporarily stopped and both were later cured by much larger doses of antibiotics. This shows the importance of giving fully adequate doses from the start.

The Practical Procedure of Treatment with Penicillin

There can be no discussion of treatment without first emphasizing the importance of early diagnosis. When vegetations are small and the gross destruction and deformity of the late lesions is not yet present, thorough treatment may leave the patient as well as he was before the infection. Every person with signs of a valve lesion or of a congenital defect should be scrupulously watched by his physician for early evidence of bacterial endocarditis.[25] In the aged especially,[26] symptoms may be mild and indefinite and fever very slight, so that the diagnosis of endocarditis is easily overlooked. During the course of respiratory or certain other infections and in connection with dental extraction or oral surgery special care should be taken, and prophylactic injections of penicillin should be generously used.[27, 28] With tooth extraction penicillin should be given not only before the operation but for several (four to six) days thereafter in full doses. The frequency of onset of bacterial endocarditis following dental procedures fully justifies such an effort.

When the diagnosis has been confirmed and the sensitivity tests have been completed, treatment should be systematically planned. The type and extent of the lesions, the general cardiac condition, the degree of fever, the presence of embolic or other complications, must all be considered in deciding whether bed rest is obligatory or whether activity should be allowed. We consider it safer, if possible, to start therapy in the hospital and at bed rest. After a week or two, if all is going well and the basic heart condition allows, mild activity may be permitted. We have never regretted being conservative on this point.

The intravenous and subcutaneous routes for administration of penicillin have long been discarded and intramuscular injections are always used. So, too, we have abandoned all oily preparations and employ either crystalline penicillin or slowly absorbed aqueous procaine penicillin. Even in patients with a highly sensitive strain of *S. viridans* we use at least 600,000 units daily; the total can conveniently be given in two injections at 12 hour intervals and such therapy has invariably been adequate. In cases with resistant strains where much larger amounts of penicillin (6,000,000 units or more) are required, it seems advisable to break the total into six or eight injections, in which case plain penicillin G is perhaps simpler to administer. However, my associates[28] in a resistant case gave single intramuscular injections of aqueous procaine penicillin G of 1,200,000 units (4 cc.) at three to six hour intervals so that in 27 days the total quantity administered was 165,000,000 units in 550 cc.

The question of anticoagulants has led to rather strong partisan feelings. It has not been our practice to use them and thorough analysis of the problem by Priest, Smith and McGee[29] led them to feel that anticoagulants probably did not prevent major embolism but merely added some difficulty and risk to an already complicated situation.

Results with Penicillin

During the past few years there have appeared numerous excellent papers[30] on the results of treatment of bacterial endocarditis with penicillin. It would serve no useful purpose, however, to attempt to analyze statistically the figures given in these reports since the clinical material and treatment programs varied widely and the total number of cases is still not large. The nature and extent of the antecedent lesion, the amount of cardiac reserve, the sensitivity of the infecting bacteria to penicillin, the age of the patient, the length of time between infection and start of treatment, for example, all play a part in determining the outcome as well as the actual scheme of therapy. It will be more useful, therefore, to discuss the results achieved in various types of cases.

All agree that the most favorable patient is the fairly young individual with a slight valve lesion or a mild congenital defect such as a patent interventricular septum in whom early diagnosis of bacterial endocarditis is made and whose strain is highly sensitive to penicillin. In patients of this sort one may predict practically 100 per cent permanent cures without noteworthy deterioration of cardiac function when 300,000 to 600,000 units of penicillin per day are given for 30 days. The usual course of

events in such cases is quite constant. Within 24 hours the patient usually declares that he feels better. Malaise and other toxic symptoms abate often with amazing speed. At the same time fever usually subsides so that an essentially normal level is reached within a day or two. At times unexplained rises of temperature may be noted for some time[20]; their exact nature is not clear. Release and absorption of tissue products in connection with resolution of vegetations must be considered. The blood culture usually promptly becomes negative and thereafter no more bacteria can be recovered from the blood stream. As a rule, within a week the patient who has no great impairment of cardiac function feels perfectly well and begins to chafe at restraint of his activity. It must be emphasized, however, that hazard of embolic phenomena, of perforation or rupture of valves persists for some time, in our experience at least as long as 50 days after therapy is started. Some of the greatest disappointments have occurred in patients doing well when a late hemiplegia or other accident takes place. We have had no chance to fully appraise the effect of penicillin therapy on the renal lesion, a problem which deserved very careful exploration, but the possibility of progressive renal damage is another strong argument for early diagnosis and thorough treatment. The following case illustrates how easily the infection may at times be extirpated with small doses of penicillin; it also shows the subsequent excellent prognosis:

An 18 year old girl had had rheumatic fever at the age of 10. She was left with a heart murmur but was essentially well. About four months before entry, in April 1944, she developed fever, malaise, joint pains and palpitation. Seven blood cultures were reported positive for *S. viridans*. She did not appear very ill. There was moderate fever. There were signs of a mitral lesion and blood culture again yielded *S. viridans*, which was inhibited by 0.05 unit per cc. of penicillin. There were a few petechiae, but the spleen was not felt. There was no evidence of a renal lesion. She received 300,000 units of penicillin daily by intravenous drip for eight days and slightly smaller amounts for the next three days. Thereafter, intramuscular injections were given every three hours totalling only 120,000 to 200,000 units daily. Total penicillin was only 10,000,000 units over 60 days. There was a prompt drop of temperature to normal and she felt very well. The blood cultures immediately became negative and remained so. She left the hospital clinically well, but with the cardiac signs unchanged. This patient has been carefully followed and was last seen in May, 1949, five years after the conclusion of therapy. She was perfectly well and had had two successful pregnancies. There was no evidence of deterioration of cardiac reserve and the physical signs were exactly as described on the first entry.

This case illustrates beautifully the very small amounts of penicillin which may be adequate to cure bacterial endocarditis and the preservation of cardiac function if the infection is treated early. Today, however, we would probably give a case like this 600,000 units daily of procaine penicillin in two doses over a period of a month.

Patients with badly damaged valves and with limited cardiac reserve have a much worse prognosis. Here again bacterial sterilization is usually readily achieved if the strain is sensitive but victory gives way to defeat when cardiac failure supervenes. This whole question has been thoroughly analyzed from our clinic by Fiese.[31] He found in the 30 per cent of our treated patients who subsequently developed failure that the following factors were of importance: age, the type of cardiac lesion, previous cardiac reserve, x-ray appearance of heart, length of time until treatment, the height of the fever, degree of bacteremia and care of heart after treatment. The situation is therefore very complex. In several of our cases there has been some suggestion that the type of healing which goes on under penicillin may in itself lead to distortion of valves so as to promote later cardiac failure. In the case reported by Carnes and Tinsley for example,[18] the mitral valves post mortem were mere fibrotic nubbins. Similar experiences have been noted by Rosenblatt and Loewe[32] and others[33] who also have been disappointed when cardiac failure developed in cases bacteriologically cured. Here, then, is another strong argument in favor of early diagnosis and prompt therapy before great damage has occurred.

The following case illustrates cardiac failure following otherwise successful therapy.

A 34 year old man, an accountant, had had polyarthritis at the age of 15. A heart murmur was known to have been present since then. Five months

before entry in 1944 he developed an indefinite febrile illness. There were typical signs of mitral stenosis, a palpable spleen, clubbing, and petechiae. There was evidence in the urinary sediment of a mild glomerulitis. Blood culture yielded nonhemolytic streptococci. Treatment consisted of a total of 9,500,000 units of penicillin, intravenously for 18 days, intramuscularly for 32. He gained 20 pounds and changed from what appeared to be a dying man to one who seemed perfectly well, and the blood cultures remained sterile. The heart murmurs persisted and the pulse was slightly rapid. The signs of the renal lesion disappeared. He had no symptoms of failure at all before treatment but as soon as he became active after treatment there were tachycardia and slight shortness of breath on effort. Cardiac incompetence progressed, the heart enlarged, he developed frank failure and took his life nine months after discharge.

It was the impression that a man only 34 years old with an asymptomatic lesion would not have progressed to failure as rapidly as this man did had it not been for the infection. Although there was no recurrence of bacterial endocarditis one wonders whether, in the process of healing, shrinking and damage did not take place which contributed to his rapid failure.

The Management of Cases Associated with Resistant Strains of S. Viridans

A great deal of work has been done on classification of strains of *S. viridans* isolated from cases of subacute bacterial endocarditis.[34–36] An excellent discussion is also to be found in Swift's recent article.[37] It seems that, whereas most cases of bacterial endocarditis are caused by streptococci of the viridans group, about 10 per cent have infections with streptococci of group D, especially the so-called enterococci or *S. fecalis.* These organisms are usually extremely resistant to penicillin in the test-tube. Ten to 50 or more units per cc. of medium may be necessary to inhibit their growth and a corresponding refractoriness to therapy is usually noted. Especially discouraging in patients falling into this group is the fact that intensive treatment often produces an apparent cure, temperature falls, the patient feels well and the blood cultures are sterile; but no sooner is penicillin discontinued than bacteremia returns together with fever and symptoms. Such suppressive therapy must always be looked for in the enterococcal cases. To cope with this situation adequately, therefore, the physician must recruit all his resourcefulness and ingenuity. Stratagems which may be successful are (1) the use of huge doses—up to 20 million units daily of penicillin, (2) measures to raise blood level of penicillin by delaying urinary excretion, (3) combinations of several antibiotics such as penicillin and streptomycin. Clark, Bryner and Rantz[19] in our clinic have made an intensive study of the problem and were able to cure eight out of nine patients with endocarditis caused by unusually resistant streptococci of various groups. One case, for example, whose organism, an enterococcus, required 10 units penicillin per cc. of medium for inhibition, received first six million units and then twelve million units daily, a total of 600 million units being administered in 50 days. This patient had a renal lesion which delayed excretion of penicillin so that blood levels of 100 units per cc. were achieved, which no doubt helped in promptly extirpating the infection. In another patient alternate courses of penicillin and streptomycin failed to reverse the blood culture and the organisms became more and more resistant so that finally 3.2 units per cc. were required for inhibition. After several months of failure the infection was at last readily eliminated by raising the dose of penicillin to 8 million units daily. This patient is well four years later.

We have made no purposeful attempts to raise penicillin blood levels by blocking urinary excretion with caronamide or paraaminohippuric acid but have depended more on large doses of antibiotics. However such blocking is quite rational and may well turn out to have a useful place in therapy if a really satisfactory agent can be found.

The Combined Use of Penicillin and Streptomycin

Robbins and Tompsett[38] recently made the interesting observation that patients with enterococcal infection resistant both to penicillin and to streptomycin were easily cured by a combination of the two in relatively small doses. Several patients who received six million

units of penicillin and 2 Gm. of streptomycin daily promptly had their bacteremia reversed and did not relapse over a 12 month period. One of our own patients in whom a brilliant result was achieved by this useful stratagem is briefly reported.

A 23 year old woman, previously well, induced an abortion in February, 1949, and entered the hospital on April 10. Two weeks previously she noticed fever in the evening. There were no other symptoms, but blood culture was said to show *S. viridans*. On examination the heart was rapid and first sound at apex was replaced by a short, rough systolic murmur. Numerous blood cultures yielded nonhemolytic enterococci which required 5 units of penicillin for test tube inhibition and were not inhibited by 50 μg. of streptomycin. In view of the high resistance of the organisms it was decided to try aureomycin. Four Gm. were given daily by mouth supplemented by two intravenous injections of 100 mg. each for seven days. Although temperature fell to normal and she felt well, enterococci continued to be present in numerous blood cultures. It was therefore decided to try a combination of 5 million units of penicillin and 2 Gm. of streptomycin daily. On the day after this treatment was started blood culture was negative and continued so on many occasions. After two weeks treatment was stopped, blood cultures remained sterile and the patient was clinically well. She was last seen in December, 1949, nearly six months later, and was perfectly well with negative blood culture, but the systolic murmur persisted.

The Use of Streptomycin Alone

It must not be forgotten that occasional cases of subacute bacterial endocarditis are caused by a variety of bacteria other than *S. viridans*. Some of these organisms are highly refractory to penicillin but may be sensitive to streptomycin. It has become a routine procedure in our laboratory to test all bacteria isolated from endocarditis cases for sensitivity to both penicillin and streptomycin; the clinician may then selected the antibiotic or combination which he considers most suitable. The use of streptomycin is reviewed by Hunter[39] who found it useful when penicillin failed in bacterial endocarditis caused by gram-negative bacilli, enterococci, staphylococci and other organisms. Others[40, 41] report instances of endocarditis caused by bacterioides in which streptomycin was of value.

Aureomycin and Chloromycetin

Curiously enough neither aureomycin nor chloromycetin seems to have been widely explored in the therapy of bacterial endocarditis in spite of the obvious advantage or oral administration. We have found few actual reports,* and no doubt the great effectiveness of penicillin has discouraged use of other drugs. There seems little doubt, however, that endocarditis caused by strains highly sensitive to aureomycin would be readily cured. Our own experience is confined to 2 patients resistant to penicillin in whom aureomycin was tried without success. The first was the patient with postabortion enterococcal infection already mentioned. The second, also with an enterococcal infection, had a strain which was completely inhibited in vitro by 0.1 μg. of aureomycin per cc. In spite of this, blood culture remained positive during five days on which he received successively 2, 4, 4, 6, and 8 Gm. of aureomycin by mouth. He was eventually cured by huge doses of penicillin.

No doubt still other antibiotics will be developed in the future which will be valuable in bacterial endocarditis. My colleague, Dr. L. A. Rantz, has, for example, treated a case of bacterioides endocarditis not cured by penicillin, aureomycin and streptomycin with a new antibiotic, terramycin. The organism was

* Brainerd and co-workers (J. Clin. Investigation **28:** 992, 1949, Part 1) report, without details, that in 2 cases of subacute bacterial endocarditis caused by *S. fecalis*, fever and bacteremia disappeared during treatment with aureomycin but recurred after the drug was stopped. Long and associates (California Med. **70:** 157, 1949) also allude briefly to the cure of a child with *S. fecalis* bacterial endocarditis by aureomycin. Harvey, Mirick and Schaub (J. Clin. Investigation **28:** 987, 1949, Part 1) report the cure of an *S. fecalis* infection at the site of suture after a Blalock operation on a child. In 3 other cases evidence of infection persisted during or after treatment even when 6 or more Gm. of aureomycin were given for several weeks. From these reports and from various personal communications it is suggested that aureomycin is on the whole less effective than penicillin but many more long-time observations are necessary to draw final conclusions. In some cases patients are unable to take adequate doses by mouth for a long enough period and suppressive effects are followed by relapse.

highly sensitive to this material and was inhibited by 1.0 μg. per cc. Terramycin, in doses of 0.5 Gm. by mouth every four hours reversed the blood cultures, and the patient seems to be cured.

Reinfections

As large numbers of cured cases of bacterial endocarditis have accumulated in the past few years it is evident that reinfection must sooner or later be observed. Herring and Davis[42] reported a patient who recovered from two separate episodes of infection separated by 20 months of apparent good health. Rosenburg[43] also describes a man who reappeared nearly two years after cure of *S. viridans* bacterial endocarditis with another infection which was again extirpated by penicillin. Whether the organism in the second attack represented an entirely new infection, or whether even after such a long interval of "cure" some bacteria which remained dormant deep in a scarred valve renewed their activity, is an interesting point. We have seen 2 patients who had second attacks of this sort; in one of them it was suggested that the same strain was operative on both occasions.

An 18 year old girl had had a long bout of active rheumatic fever six to seven years ago. Subsequently a loud, rough, systolic murmur was noted and she was followed in this clinic. The heart became considerably enlarged and her pulse tended to be fast but there was no gross failure. About six weeks before entry on Feb. 1, 1946 she had fever, malaise, and aches and pains. Culture for *S. viridans* was said to be positive. She was pale and thin, the heart was rapid and there was a loud, harsh, systolic murmur maximal at the apex. Blood culture yielded 15 colonies of nonhemolytic streptococcus which grew well in the presence of 0.05 unit of penicillin per cc. but was inhibited by 0.1 unit per cc. One hundred thousand units of penicillin was given every six hours—400,000 per day. Temperature, previously elevated to 38 to 29 C., promptly fell and blood cultures became negative. On the nineteenth day of penicillin, however, a positive blood culture was again obtained. The dosage schedule was then changed to 50,000 units every three hours. This was continued until the sixtieth day. Five blood cultures were subsequently negative, and she was discharged as cured of her infection in May, 1946.

She was carefully followed and remained essentially well with no signs of recurrence for nearly two years. On March 29, 1948, she returned with complaint of fever, malaise, and joint pains for two months. Physical examination was about as before but the spleen was now palpable and the temperature ranged from 37.5 to 38.5 C. Blood culture yielded 20 colonies per cc. of a nonhemolytic streptococcus. The strain isolated on the previous entry was not available but the new strain bore a striking resemblance to it. The degree of sensitivity and the cultural characteristics were the same. This could hardly be a coincidence and the question was raised as to whether the second attack, even after the long interval, was not a recrudescence with organisms which had lain dormant in the damaged valve rather than a new infection with a different strain. This time she again received treatment for 60 days consisting of two daily injections of 600,000 units each of Duracillin, a slowly absorbable penicillin preparation. All cultures were subsequently sterile and when last seen in February, 1950, nearly two years later, she was in good condition with no further signs of recurrence.

Several important facts are brought out by this case. First we are in the unsatisfactory position of not being certain whether the second attack was a recrudescense or an entirely fresh infection. It becomes clear that in order to settle such a question in future cases it is essential for laboratories carefully to preserve all endocarditis strains so that should a second attack occur an actual comparison can be made. Secondly it is of interest that in the first attack 400,000 units of penicillin per day in four doses proved subcurative, whereas the same total daily quantity given in eight doses was effective.

In the second patient, a 69 year old man whom we had cured of *S. viridans* endocarditis in 1945, a prostatectomy done in 1948 was followed by an enterococcal implantation, obviously an entirely new infection.

Discussion and Summary

In the preceding pages we have outlined the development of treatment of bacterial endocarditis with antibiotics. A good deal of stress has been placed on our own work and that of our associates; it has been an exciting experience to observe the improvement in methods and in results since the early days of penicillin therapy six years ago.[44] The following points are especially to be emphasized.

First of all, the great importance of early diagnosis, before huge deforming and destruc-

tive vegetations have grown, cannot be overstressed. In early cases therapy often leaves the patients in essentially as good condition as before the infection.

Second, it must be recognized that penicillin does not prevent cardiac failure and that many patients whose infection has been cured will die in decompensation or because of an embolic accident or disturbance of cardiac mechanism. Renal failure may be a serious problem in some cases.

Third, there should be emphasized the necessity of making every effort to isolate the causal bacteria and of performing accurate sensitivity tests. It is only with this information at hand that the most promising antibiotic and the proper dosage can be selected.

Finally it is pointed out that most patients with highly sensitive strains of *S. viridans* can be readily cured by small daily doses of penicillin but that, because of the nature of the lesion, therapy should be continued for at least four weeks in order to prevent recrudescences. On the other hand resistant strains challenge the ingenuity and resourcefulness of the clinician and demand huge doses of antibiotics.

While an unsurpassed therapeutic triumph has already been achieved in the ready cure of bacterial endocarditis, no doubt even more effective and more readily administered drugs will be developed in the future.

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Electrical Impedance Plethysmography

A Physical and Physiologic Approach to Peripheral Vascular Study

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The quantity of blood measured by electrical impedance plethysmography is defined by its resistive effect in parallel to the resistance of other tissue of the segment. By substitution of this parallel resistive value, together with data relative to the resistivity of blood and the length of the segment in the formula for the volume of an electrical conductor, we are able to derive the volume of the pulse in cubic centimeters. It follows that the volume displaced from the venous reservoir and the rate of refilling of the venous reservoir of an extremity may also be determined quantitatively.

NUMEROUS attempts and methods have been evolved to measure pathologic and functional vascular change in the extremities. Little attention, however, has been given to the quantitative changes recordable by various methods of electrical plethysmography,[1–5] which until recently have been difficult to formulate. The current presentation deals principally with the calculation and interpretation of volemic changes in the extremities as they appear measurable by electrical conductivity.

The electrical conductivity method gives a physical measure of the ionic conduction of a given body segment in contrast with electronic conduction characteristic of metallic substances. An attempt will be made to restate and formulate the laws of electrical conduction as they appear applicable to changes within a body segment which is being studied by the passage of a radio frequency current. As has been shown elsewhere,[6] transient and static values of electrical conductivity are associated, respectively, with dynamic and balanced conditions of arteriovenous blood volume differences within a given segment.

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METHOD

A differential electrical impedance bridge operating at 150 to 200 kilocycles, as described elsewhere,[6] is used as the basic instrument for measurement of small and large variations in volume of the extremities.

In this study, our measurements on human extremities are made with aluminum foil strips 1 cm. wide, mounted on a gummed tape 2 cm. wide. After wetting the foil with a concentrated salt paste (nondrying), the electrodes are applied firmly without preliminary massage or washing. This tends to avoid local circulatory reactions which may modify our measurements. The electrodes are usually applied circumferentially and held loosely by a clip lead to avoid constriction (fig. 1).

There appears to be an inherent advantage in a four electrode technic as shown later. The two outer electrodes (I_1 and I_2) are used for applying the current, and the two inner electrodes are used for delineating the segment under measurement. The inner edge of the E_1, E_2 pair is the effective edge of the segment for measurements of the limb. Most of the measurements reported here are based on a conventional two electrode method represented by the E_1, E_2 pair to which the current is also applied under such conditions.

The standard for comparison of the segmental pulse volume resistivity is usually .05 to 0.1 ohm resistance. One ohm is used for comparison of large changes in segmental blood volume. A small percentile change of the total substitution resistance for the segment is also adaptable as a standard.

The Physical Basis and Elementary Considerations in Electrical Volume Recording

The electrical impedance pulsation represents a changing number of ions brought to the segment by the arterial stream at a rate exceeding the venous outflow during the cycle. The over-all change in volume of a segment is the differential effect of expansion and emptying of the vascular components of the entire segment.

It may be possible to account segmentally for the volumetric shift of blood by considering its effect as a variable parallel electrical shunt. Equations for the effect of parallel resistance are well known.

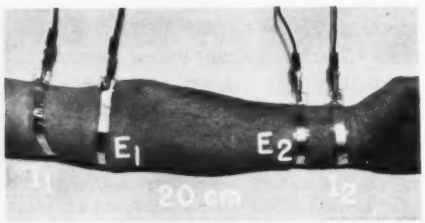

Fig. 1. A photograph of the forearm illustrates the manner of applying the aluminum foil electrodes. The arrangement is tetrapolar. The inner electrodes are designated E_1, E_2, and the outer electrodes I_1, I_2. The segment of 20 cm. in length between E_1 and E_2 is the effective resistance (R_0).

The total electrical conductance of the extremity segment is probably equal to the sum of the paralleled conductances of the blood and segment proper. Each additional pulse of blood represents another path through which electrical current will flow.

The effective parallel resistive value of the added or displaced blood may be derived by substitution of measured values in the expression:

$$R_B = \frac{R_N R_0}{R_0 - R_N}, \quad \text{or} \quad R_B \approx \frac{R_0^2}{\Delta R} \qquad (1)$$

in which R_0 represents the original resistance of the segment, R_N, the new total resistance. $R_0 - R_N$, which is equal to ΔR, represents the change in resistance incurred by the change in blood volume of the segment, by pulsation or otherwise. When small volume and resistive changes occur, then R_0^2 expresses essentially value of the product $R_N R_0$.

The volume of blood within the segment is a direct and linear function of electrical conductivity. This is true within wide limits of expansion of elastic cylinders such as arteries, veins, intestines, and rubber tubes, as shown elsewhere[6] by one of us (J.N.). The inclusion of ground meat, long bone, or ground bone changes the slope of the relationship but does not destroy the lineal effect.

The change in volume of blood uniformly distributed within a segment may then be calculated from the derived expression of the volume of a cylindrical conductor:

$$V_B = \rho \frac{l^2}{R_B} \qquad (2)$$

in which ρ represents the specific resistivity of the segmental blood, l the length of the segment being measured, and R_B the calculated effective parallel resistance of the blood related to the change. Compare equation 1 in *Medical Physics*, Vol. II, p. 738.

Direct comparison of the impedance and sensitive mechanical plethysmographic records of the volume pulse of the finger published elsewhere[5, 6] shows no apparent discrepancy between the forms of the curves recorded at approximately the same amplitude. They appear identical, and this suggests the similarity of origin to the volume pulse of the segment.

The Measurement of the Volume Pulse

The volume of blood pulsed into a peripheral segment is usually equal to the volume of blood leaving during the cycle. If one had an accurate measure of either the input or output, or of both volumes, it is probable that valuable data covering vascular responses could be scientifically expressed. If a measure closely proportional to the absolute pulse volume were obtained, it would not be necessary to know either phase of the volume change.

Segmental blood flow can be approximated at present by the venous occlusion plethysmograph.[7, 8] This method is objectionable since the pressure of occlusion may modify the vascular responses and other factors beyond reasonable control. If, under these conditions of

measurement, one also knows the pulse rate, the pulse volume may be deduced from such data.

Since there is usually a continuous venous run-off from the segment during the cycle, it is apparent that the recorded volume pulse is the net difference between a momentary excessive arterial input and the run-off of blood, whether it be venous or arterial, during the cycle in the absence of stasis.

If the above events are true, the recorded pulse volume is directly proportional, but not necessarily equal to the sum of the true arterial inflow and the venous outflow from a given segment. It follows that the mean height measurement[6] of the pulse wave should be a valid index of this proportional volume. In our study, twice the mean height for the area under the curve is chosen to represent both input and output volume. In effect, this represents a sequestration of the total segmental input without occlusion or run-off of the venous return.

In practice, one obtains the mean height of the pulse volume by planimetric integration over the entire pulse distance. The measurement of several pulses serves to reduce the error. This value is multiplied by two, since the recorded volume increase served both as a measure of input and of output volumes during the entire pulse cycle.

This measured value is then interpreted in terms of ohmic resistance based on comparison with the 0.1 ohm standard recorded in the original trace or in the records with the equivalent substitution of resistance. This value in ohms represents ΔR of equation 1. As one has measured the approximate substitution resistance (R_0) for the extremity conductor before the pulse volume modified the conductor, one may then derive R_N arithmetically.

The effective parallel shunt, R_B, is then calculated from the known values (R_N, R_0, and $R_0 - R_N$) by equation 1.

The calculation of pulse volume is completed by equation 2. In addition to R_B, one must know the other measurable units defined in this equation. We will assume that the measured resistivity of nonflowing venous or arterial blood will supply the factor ρ. Theoretically, this may be different for each individual. Its value is in the order of 145 $\pm$ 3.75 S.E. ohm cm. at 37.5 C. measured at 175 kilocycle frequency. We assumed a value of 150 ohm cm. for many of our measurements. The derived pulse volume multiplied by the heart rate gives the proportional volume of expansion of the segment in cc. per minute. If one knows the volume of the segment, it is possible to express proportional expansion in terms of volume per minute per 100 cc. of segment.

The volume of the peripheral segment is never an ideal cylindrical conductor for which the equations were designed. Some corrections should probably be made for the shape of the conductor. Cole and Curtis[9] have discussed this factor in relation to cell models.

Comparative measurements of similar segments on opposite limbs obviate many of the difficulties due to shape and enhance the value of our observations in a limited number of cases.[10]

Results

Bipolar and Tetrapolar Resistive Measurements of a Body Segment Including the Skin

Horton and van Ravenswaay[11] and Barnett[12] have shown that the reactive component of electrical impedance is very high in skin compared to its value in deep tissues. If this is true, then it appears that the determined values for impedance of a segment in which the deep tissues predominate in volume are probably too high by bipolar measures. Since the total impedance of the segment enters into the calculation of the parallel resistance, the value of mean pulse volume would probably be in error.

In table 1, column R_0 shows that for equal segments, the four electrode method gives consistently lower values for total segmental resistance than the two electrode method. No attempt was made to measure at controlled conditions of rest, exercise, postprandial time, or room temperature. The subject was recumbent.

The four electrode method basically eliminates the highly reactive skin and leaves one with a better measure of the internal tissues, including the blood, which appear predominantly resistive to alternating current. The pulsatile volume should probably be calculated

on the resistive values obtained by tetrapolar leads, if a closer approximation to the true proportional pulse volume is desired.

Column $R_0 - R_N$ or ΔR represents twice the mean height of the pulse expressed in ohms. It appears that no consistent prediction can be made of this value under the conditions of measurement (but at no time do these exactly equal each other).

The value, however, for the parallel resistive effect (R_B) of the blood pulse volume is predictable and consistent. Each of the tetrapolar legs electrically shunted in parallel are shown (table 2). The value for the total resistance of both legs is predicted to be 38.1 ohms; however, by measurement, we obtained 37.2 ohms, which is reasonable. For mean change in pulse height, we predicted .0187 ohm and obtained .0191 ohm. For calculated volume changes, we predicted .773 cc. and obtained .828 cc. for pulse volume. We predicted 47.4 cc. and obtained 50.8 cc. for pulse volume per minute. Similar values are shown for predicted and measured parallel resistances and parallel pulse

TABLE 1.—*Comparative Resistive Values of Pulse Volume by Bipolar and Tetrapolar Measurement**

Segment (Recumbent)	Length (cm.)	R_0 (ohms)	R_N† (ohms)	$R_0 - R_N$ (ohms)	$R_B \times 10^5$ (ohms)	Pulse Volume‡ (cc.)	Pulse Rate	Minute Volume (cc.)	Room Temp. (C.)	Time (min.)
Four Electrode Studies										
Right forearm.....	20	86.7	86.58	.120	0.626	.959	56.6	54.3	27.5	3
Left forearm.....	20	95.9	95.789	.111	0.824	.728	56.6	41.2	27.5	9
Right forearm.....	20	90.7	90.611	.0894	0.898	.668	54.1	36.1	27.3	14
Left forearm.....	20	96.1	96.024	.076	1.214	.494	54.1	26.7	27.1	18
Two Electrode Studies										
Right forearm.....	20	99.5	99.383	.117	0.844	.711	57.7	41.0	27.5	0
Left forearm.....	20	108.5	108.38	.115	1.02	.589	56.6	33.3	27.5	5
Right forearm.....	20	103.6	103.50	.0986	1.09	.552	56.6	31.2	27.3	11
Left forearm.....	20	110.2	110.12	.0769	1.58	.380	57.7	21.9	27.0	21

* In this experiment a progressive change in measurements is shown with time. This is probably physiologic rather than physical in origin. Premeasurement period of rest may have been inadequate. The decreased minute volume with time is suggestive of peripheral vasoconstriction which occurs with the change to a recumbent posture.

† Probably no more than three or four figures at any time are significant in columns designated R_N in this and subsequent tables. They merely illustrate the influence of the shunt due to the pulse. For practical purposes in calculation of pulse volume, R_N equals R_0.

‡ Resistivity of the blood assumed as 150 ohm cm.

measurements is lower than the corresponding bipolar measurement of a given arm.

The resultant effect on the calculation of pulse volume shows that tetrapolar measurements give higher values than bipolar measurements.

It follows that the values for pulse volumes per minute in our data are significantly higher for the tetrapolar method in spite of slightly higher pulse rate during the bipolar measurements in the reported experiment (table 1).

Parallel Impedance of Two Similar Segments as a Measure of Parallel Pulse Volume

The effect of electrically parallel circuits is defined by equation 1. The resistive values for study of the left leg, the right leg, and of both volume studies in the arm segment (table 2 and figure 2).

A bipolar technic was employed because the four electrode method was not available at the moment. Perhaps a better correlation may be obtained with more careful control. The experiment proves that we may study complex biologic electrical impedances, such as the blood pulses, in parallel, and predict the final impedances and the parallel segmental expansion due to blood with fair accuracy, under changing physiologic conditions.

External Parallel Shunts on the Skin between the Effective Electrodes

The summary of such an experiment is tabulated and shown (table 3 and fig. 3). It is noted

TABLE 2.—*Parallel Impedance Study of Two Similar Segments*

Segment (Recumbent)	Length (cm.)	R_0 (ohms)	$R_0 - R_N$ (ohms)	$R_B \times 10^5$ (ohms)	Pulse Volume* (cc.)	Pulse Rate	Minute Volume (cc.)	Room Temp. (C.)	Time (min.)
Study of Two Legs on Subject J. N.									
Left leg	20	76.5	.0382	1.53	.392	61.3	24.0	21.0	0
Right leg	20	75.8	.0367	1.57	.392	61.3	24.0	20.8	48
Both legs in parallel—measured	20	37.2	.0191	0.725	.828	61.3	50.8	21.0	44
Both legs in parallel—predicted	20	38.1	.0187	0.776	.773	61.3	47.4	21.0	24
Study of Two Forearms on Subject M. K.									
Right forearm	20	144.5	.1069	1.95	.307	75.0	23.0	23.0	0
Left forearm	20	157.9	.1617	1.54	.390	65.2	25.4	23.0	3
Both forearms in parallel—measured	20	74.7	.0781	0.714	.844	69.7	58.8	23.0	6
	20	74.7	.0617	0.831	.721	70.1	51.6	23.0	8
Both forearms in parallel—predicted	20	75.5	.0650	0.861	.697	69.9	48.7	23.0	1.5

* Resistivity of blood assumed as 150 ohm cm.

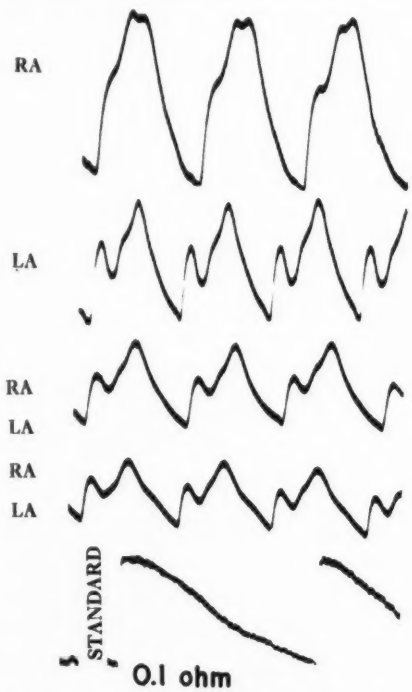

FIG. 2. The parallel effect on the pulse volume of combining resistive changes in the right arm (RA), and left arm (LA), is shown in the third and fourth curves. The calculations are outlined in the text and table 2, subject M.K. An A.C. coupled amplifier controls the terminal oscillograph. The drift shown in the standardization curve is characteristic of the end recording equipment.

that the total resistance (R_0) of the leg segment drops from 75.8 ohms to 71.7 ohms on application of salt paste between the electrode region. A further drop to 52.9 ohms occurs on wrapping a sheet of aluminum foil around the midsection of the measured segments. Later, by calculation, it appeared that the effective parallel resistance of the salt and aluminum foil (surface shunt) was 175 ohms.

The influence of salt paste on the final pulse volume because of its coldness appears to have resulted in a slight reduction of 1.3 cc. per minute from a level of 24.0 cc. per minute for the segmental expansion.

The addition of aluminum foil over the salt paste was followed by measurement six minutes later. These values showed an increase in pulse volume and minute volume. The level exceeded the paste study by 6.1 cc. and the control level by 4.8 cc. The change was not due to room temperature, which was constant. The subject complained of a feeling of warmth under the aluminum foil. The change might have been due to local changes interfering with radiation of heat from the segment. It is improbable that the physical application of a shunt resistance of 175 ohms in parallel with the leg was the cause of physiologic changes. It is concluded that physiologic changes in pulse volume and minute volume are secondary to the peculiar method of producing the physical shunt.

By further experiment under controlled conditions, an external physical shunt of 200 ohms parallel to the blood circulation and the tissues of an extremity did not produce a physiologic change, but the anticipated physical effect of

TABLE 3.—*The Effect of a Low-Resistive Parallel Shunt on the Skin Between the Electrodes on the Resistance and Volume Pulse*

Segment (Recumbent)	Length (cm.)	R_0 (ohms)	$R_0 - R_N$ (ohms)	$R_B \times 10^5$ (ohms)	Pulse Volume (cc.)	Pulse Rate	Minute Volume (cc.)	Room Temp. (C.)	Time (min.)
Right leg (control)	20	75.8	.0367	1.57	.392	61.3	24.0	20.8	0
Right leg covered with paste	20	71.7	.0318	1.62	.370	61.3	22.7	21.0	8
Right leg covered with aluminum foil	20	52.9	.0223	1.25	.479	60.0	28.8	20.8	14
Right leg after aluminum foil and paste removed	20	77.8	.0373	1.62	.371	63.8	23.6	21.0	32

The calculated effective parallel resistance of the aluminum foil and the electrode salt paste is 175 ohms.

Subject (J. N.) stated that the paste felt cold while the aluminum foil covering the leg produced a warm feeling which may account for some shift in minute volume.

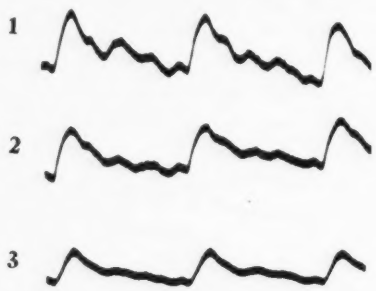

FIG. 3. The shunting effect, between bipolar electrodes, of smearing a salt jelly over the skin is shown by reduction of pulse amplitude (2) in comparison with control pulses (1) from the right lower leg. A still greater surface shunt is produced by adding aluminum foil about the segment (3). All curves are recorded at the same sensitivity of the instrument. See text and table 3.

reducing the recorded pulse volume was evident and predictably reproducible.

Mild Exercise and Pulse Volumes of the Forearm Segment

Subject E. T. was studied before and after one minute of flexion and extension exercise of the fingers, using the bipolar method on the forearm. The results are shown (table 4) and indicate a significant rise in the calculated pulse volume and minute volume by impedance methods on the same arm. There is an evident return to normal pulse volume and minute volume within six minutes. A change from 19.9 cc. to 26.0 cc. per minute is shown after one minute of exercise of the same type in one forearm of subject J. N.

It appears from limited data that the vascular expansion may be differentiated as to exercise in the extremities as shown in the forearm segment under controlled conditions by electrical impedance studies.

TABLE 4.—*Physiologic Response in Pulse Volume to Exercise**

Subject (Recumbent)	Length (cm.)	R_0 (ohms)	$R_0 - R_N$ (ohms)	$R_B \times 10^5$ (ohms)	Pulse Volume† (cc.)	Pulse Rate	Minute Volume (cc.)	Room Temp. (C.)	Time (min.)
Subject E. T.									
Forearm before exercise	20	132.0	.0713	2.44	.246	56.2	13.8	20.0	0
Forearm after exercise	20	126.0	.0874	1.82	.330	57.7	19.1	20.0	1
	20	128.0	.0862	1.90	.316	57.7	18.2	20.3	2.5
	20	128.5	.0736	2.24	.268	57.7	15.4	20.3	6
Subject J. N.									
Forearm before exercise	20	91.8	.0437	1.93	.311	63.8	19.9	20.8	0
Forearm after exercise	20	94.1	.0640	1.38	.433	60.0	26.0	21.2	1

* Exercise was moderate flexion and extension of the fingers for one minute.

† Resistivity of the blood assumed as 150 ohm cm.

Electrical Measurement of Large Changes in Venous Blood Volume of the Forearm Segment

Until recently, it has been difficult to approximate the volume of blood leaving or entering an extremity segment passively, such as may result from posture. On the basis of the foregoing changes in resistance produced by the pulse volume, we reanalyzed the type of experiment originally recorded at Wright Field.

A forearm segment was prepared as usual with two electrodes for resistive studies at a given posture. The arm was allowed to rest in a natural position and R_0 was measured by substitution. $R_0 - R_N$ or ΔR was recorded at low recording sensitivity, so that 1 ohm was equal to 5 mm. excursion of the galvanometer. This is shown in figure 4 at region 1, where there is no evidence of drift or other imbalance except the standard. The base of measurement was 165 ohms and the pulses were visible but not measurable. The arm was then raised gradually above the shoulder level as the subject was sitting. This was associated with a precipitous drop in electrical conductivity and presumably a passive decrease in the amount of venous blood stored in the veins of a given segment. This emptying of the veins is recorded opposite region 2. This was followed by a very slow rate of decrease in conductivity opposite regions 3 and 4 of the record.

When the arm was lowered moderately fast, the initial effect was to produce the wave in the conductivity record opposite region 5. This may have been associated with partial reflux or retrograde flow of venous blood which was not held back by the venous valves above the proximal electrode on the arm.

Thereafter, the return curve was more uniform at region 6 before rising asymptotically toward the baseline at regions 7 and 1. The volume of the arm and the venous reservoir had nearly refilled to the original level at regions 7 and 1, judging from the conductivity curve. Region 6 may be important as a measure of unobstructed filling of the venous reservoir.

TABLE 5.—*The Effects of Raising the Arm on the Electrical Resistance and Calculated Venous Outflow*

Subject (Recumbent)	Venous Outflow (mm.)	Standard of 1 ohm (mm.)	R_0 (ohms)	ΔR (ohms)	R_N (ohms)	$R_B \times 10^3$ (ohms)	Venous Outflow (cc.)
Left forearm	10.0	5.5	118	1.8	119.8	7.81	7.7
	8.5	4.0	118	2.1	120.1	6.75	8.9
	11.0	4.5	118	2.4	120.4	5.92	10.2
	16.0	6.0	118	2.7	120.7	5.33	11.3
	20.0	5.0	118	4.0	122.0	3.60	16.7
	21.0	5.0	118	4.2	122.2	3.43	17.5
	19.0	4.5	118	4.2	122.2	3.43	17.5
Right forearm	25.0	6.0	112	4.2	116.2	3.02	19.2
	27.0	7.5	112	4.9	116.9	2.67	22.5
	42.0	5.5	112	7.6	119.6	1.76	34.2
	42.0	5.5	112	7.6	119.6	1.76	34.2

Room temperature 27 to 27.5 C.; arm volume approximately 650 cc.; resistivity of blood assumed to be 150 ohm cm.

Data arranged in the order of magnitude for ΔR of the given segment.

The linear relation to the volume of venous outflow becomes self-evident.

It was estimated from the measurements that the drop in 7 ohms impedance was equivalent to 14.5 cc. of venous outflow from the segment by raising the arm under these given conditions. As the displacement of the segment was about 650 cc., the change in volume was calculated to be 2.23 cc. per 100 cc. of a given arm segment. Other typical results of partially controlled measurement during recumbency of a given subject, arranged according to degree of deviation in volume, are in table 5.

Record B demonstrates how repeated raising and lowering of the arm produces changes in conductivity similar to regions 1 to 7 on record A. No attempt to measure these has been made as more rigid controls of activity and posture

must be defined in order to quantitate the the events properly.

Electrical Measurement of Blood Flow Without Occlusion During Refilling of the Venous Reservoir

"Exact analysis" of physiologic change has been a difficult, tedious, and ungratifying task of measuring "blood flow" in various segments of the extremity by mechanical plethysmography following venous occlusion at the outflow region of a segment.[7, 13]

Taking advantage of the technic described in the previous section of this paper, we recorded a series of preliminary observations (table 6). Limited body rest, inactivity, recumbency, and a special position for the arm were the controls. Room temperature and time between and during elevations of the extremity, as well as the degree of horizontal elevation of the proximal electrode in relation to the angle of Louis and the body, were determined.

TABLE 6.—*The Calculated Rate of Filling of the Venous Reservoir After Rapidly Lowering the Arm Without Occlusion*

Segment (Recumbent)	Venous Filling (mm./3 sec.)	Standard of 1 ohm (mm.)	R_0 (ohms)	ΔR (ohms)	R_N (ohms)	$R_B \times 10$ (ohms)	Net Volume Flow (cc./min.)
Left forearm	2.0	4	118	0.50	117.5	2.80	42.9
	3.0	5.5	118	0.55	117.45	2.54	47.8
	2.5	4.5	118	0.55	117.45	2.54	47.8
	3.5	6.0	118	0.58	117.42	2.40	50.0
	3.0	5.0	118	0.60	117.4	2.33	51.5
	3.0	5.0	118	0.60	117.4	2.33	51.5
	3.0	4.5	118	0.67	117.33	2.10	57.6
Right forearm	5.5	7.5	112	0.73	111.27	1.74	69.3
	5.0	5.5	112	0.91	111.09	1.39	86.3
	5.5	6.0	112	0.92	111.08	1.38	87.0
	5.5	5.5	112	1.00	111.0	1.27	94.8

Room temperature 27 to 27.5 C.; arm volume approximately 650 cc.; resistivity of blood assumed to be 150 ohm cm.

The data as arranged shows the linear relationship between ΔR, the resistance change per unit time and the calculated rate of return or filling of the venous reservoir with blood.

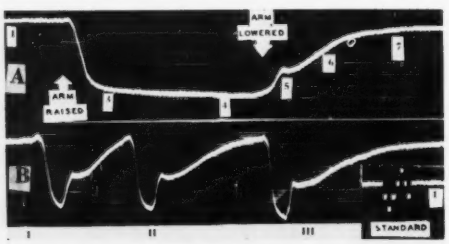

FIG. 4. The effect of raising and lowering the arm on the recorded electrical impedance of a segment of the right forearm (curves A and B). The electrical conductivity decreases and the volume of the forearm decreases as the arm is raised. See the text for further details and interpretation. A bipolar arrangement of electrodes was used for these procedures. A string galvanometer is the end recorder. The paper film speed is 6.25 mm. per second.

At region 6 of the experimental curves (fig. 4), we assumed that the fairly uniform rate of change was an index of the rate of flow of blood, refilling the recently collapsed venous reservoir of the arm segment.

We derived the results in table 6 by measuring ΔR for a portion of slope 6 as representative of the portion of blood volume (ΔV) which is filling the veins in a given time (ΔT). It is also necessary to know the equivalent parallel resistance for value ΔR, as well as the length of the segment and resistivity of the blood. Under these circumstances, substitution of values in equation 2 should permit the calculation for the change in volume (ΔV). In the illustration (fig. 4), it appears that the volume is 1.75 cc. for a period of three seconds. This represents a flow of 35 cc. per minute. This figure is reasonable for the segment of about 650 cc. volume. Further results and calculations on the same subject under better controlled conditions are arranged in order of magnitude in table 6. It appears justified to conclude that with our

technic it is possible to measure the rate of venous filling after the venous reservoir of the extremity has been collapsed by postural means. Venous occlusion may be done while the extremity is raised, in order to prevent venous outflow. Under such conditions, blood accumulates, however, immediately, and the slope often approaches the slope described in region 6 (fig. 4).

It would appear that the new technic is more physiologic and potentially as valid a measure of peripheral flow as derived by venous occlusion methods [Brodie and Russell (1905),[13] Hewlett and van Zwaluwenburg (1909),[7] and the well known modifications of these]. A comparative analysis of simultaneous impedance methods of determining blood flow is being reported elsewhere.[7, 10]

Discussion

The electrical impedance method under consideration here is not basically different from that employed 10 years ago.[4] Largely because of misunderstanding of the basic principles involved, progress of impedance measurement of the multicellular organism and its circulation has been slow and involved.

It is reasonable to assume that if there are series and parallel resistive circuits in the organism, then some of its functions may almost surely be defined in terms of resistive changes. The peripheral circulation is one of these functions. If the blood pools indefinitely or transiently within a limited segment, its resistivity will be added in some manner to the resistivity of the segment. Continuous records of electrical conductivity of a body segment trace the course of a blood volume pulse and measure its magnitude by virtue of the number and mobility of ions. If one is still in doubt on this fact, he should follow the blood conductivity of an artery in animal or man before, during, and after injection of electrolytic or nonelectrolytic substances. The dilution curve is clearly recorded elsewhere.[6] The data derived from such an observation appears to be a function of partial or complete circulation time, cardiac stroke volume, total cardiac output, and blood volume, and diffusion from the vascular system.

The various functions of the peripheral circulation which may be defined also by impedance measures are pulse volume, minute pulse volume, pulse velocity, the rate of change of pulse volume, pulse form, blood pooling and emptying, particularly of the venous reservoirs, and secondarily, the backflow into the reservoir associated with postural changes in the extremity. The rate of filling of the venous reservoir from the arterial side may be a function of segmental blood flow, as observed electrically. This long list of possibilities sounds like a copy of the encyclopedia, but in all fairness, we should find out why and where we have failed or lost our patience to define a given vascular function by electrophysical measurement.

One basic clue to evaluation of the volume of blood at any given moment in a given segment is its parallel resistive measure. To find this, we must have other data as outlined.

The concept that volume of substance is a direct function of its electrical conductivity is taught in elementary physics of conductors in relation to electronic conduction. There is no justification in believing that it does not apply to ionic conductors, such as the blood. If the blood does not alter too rapidly in its electrolyte and nonelectrolyte ratio, its conductivity should justifiably enter into volume determination as it is directly proportional to the measure of segmental volume.[6] It is not difficult to measure in vitro. If the body segment is measured at a given frequency, the blood in vitro relative to the segment should be measured at this frequency unless we have reached the infinite frequency impedance of this tissue with our signals. The physiologic conditions of flowing blood are more difficult to reproduce.

The vascular reactions to drugs, nerve block, arterial and venous occlusion, exercise, posture, anxiety, pleasure, physical agents, trauma, surgery, disease, and stimulation are but a few of the responses which may be carefully evaluated to advantage by electrical impedance methods. Burch's[8] sensitive mechanical plethysmograph has already proved to be very useful in this regard, but Goodyer[14] has recently pointed out some advantage to the electrical impedance method, although he did not show how to exact the volumetric data from his records in conventional terms.

Recently, Coulter and Pappenheimer[15] have found that turbulence in flowing blood does not influence electrical impedance measurement of blood. Thus blood cells remain oriented in turbulent flow. At low flows, however, the blood viscosity decreases with increasing flow. This effect parallels the observation of Velick and Gorin[16] who observed that the electrical resistance of flowing blood measured in the direction of flow was less than that of blood at rest. At present, we cannot supply a correction for the resistivity of blood, if a correction should be made for its flow or given velocity.

Some of the other major potential disadvantages concerned with conductivity methods are the unknown mean temperatures of the segment and its blood streams. Thermal gradients[17] are present in the arteriovenous vascular system. This presupposes differences in the conductivity of arterial and venous blood of the peripheral segment. In addition to this, the relative velocities[18] and proportion of plasma and red cells vary throughout the vascular system, and, therefore, are influential in distributing changes in resistance. Fluid shifts between the vascular and extravascular compartments also modify the electrolyte-nonelectrolyte ratio of each and incidentally the paralleled resistive effects pertaining to each. Pickering and Dow[19] ascribe consistent findings of higher relative cell volumes and plasma protein levels in venous blood than in simultaneous arterial samples to the arteriovenous shift of water from plasma to cells. These factors must be evaluated ultimately in pulsatile and nonpulsatile impedance studies of body segments, if this approach is to become a useful tool in evaluation of vascular phenomena.

Summary

1. The quantitative measure of pulse volume and the venous blood pool is defined in terms of its parallel electrical resistance to the resistance of the whole segment or of the deep tissues of the segment.

2. The parallel resistivity of a transient change in blood volume is currently evaluated by bipolar or tetrapolar methods of conduction measurement.

3. The parallel resistive value of a given pulse or a shift in segmental blood volume, together with data of the linear dimensions of the segment and the resistive value of the blood are entered into the equation for the volume of an electrical conductor to calculate the quantitative volume of displaced or new blood.

4. The pulse volume is proportional, but not necessarily equal to the true arterial inflow or venous outflow from a segment. It follows that the minute pulse volume is proportional to the segmental blood flow.

5. The physical effect of parallel circuit arrangement of both legs by experiment proves unequivocally the quantitative nature of the segmental blood pulse volume as evaluated by its parallel resistive effect.

6. It appears that the rate of blood flow in a peripheral segment may also be approximated by evaluation of the rate of filling of a previously emptied venous reservoir produced by a change in posture of the segment.

7. The electrical impedance methods appear sufficiently accurate and sensitive to warrant further consideration for application to basic and clinical medical science.

Addendum

Since the original submission of our manuscript, F. H. Bonjer,[20] in his thesis "Circulatieonderzoek door Impedantiemeting," has independently correlated the recently published equations[6] and arrived at the quantitative solution for pulse volume from electrical impedance data on extremity segments, i.e.:

$$\Delta V = -\frac{\Delta R}{R_0} \cdot \rho \frac{l^2}{R_3}$$

in which ΔV represents the pulse volume related to its maximum excursion and the other values as defined above. In effect, this is equivalent to equation 2.

At present, his impedance unit employs a frequency of 60,000 cycles and a percentile change in resistance for a standard of comparison. A tetrapolar electrode system is also used to his advantage. Open ring flexible electrodes were made from braided fine copper wire.

He also refers to Russian, French, German and Austrian investigations on body impedance, some of which were unknown to us.

Our earliest pulsatile impedance investigations[4] reported in 1940 were wholly independent of similar contributions published elsewhere.

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The Effect of Posture and of Congestion of the Head on Sodium Excretion in Normal Subjects

By J. M. Lewis, Jr., R. M. Buie, M.D., S. M. Sevier, M.D., and T. R. Harrison, M.D.

In healthy young subjects the sodium excretion is decidedly less in the sitting than in the recumbent posture. The difference can be partially overcome by compression of the neck in the sitting position. Some possible implications of these observations will be considered in the subsequent communications.

THE PRESENT study is the first of several dealing with some of the factors controlling sodium excretion in normal subjects and in patients with congestive heart failure. Only the more pertinent and recent literature will be reviewed.

One of the significant advances of recent years in regard to the nature of congestive heart failure has been the development of a concept that normal homeostatic mechanisms play an important role in the production of some of the outstanding manifestations of this disorder.[1] Thus it has been suggested that inadequacy of the cardiac output in relation to the needs of the body leads to retention of sodium, excess of extracellular fluid, hypervolemia, edema, and aggravation of congestive phenomena.[2, 3] Some have ascribed such sodium retention to decline in glomerular filtration.[4, 5] Others have considered increased tubular reabsorption the predominant factor.[6, 7]

This general concept is supported by the demonstration of decline in cardiac output (either absolute or relative to metabolic needs) in the vast majority of patients with heart failure. The demonstration that retention of sodium occurs not only during heart failure but also during peripheral circulatory failure, which is accompanied by well-marked decline in cardiac output, lends further support to this hypothesis. On the other hand, there are certain objections to this concept. Among them are:

(1) Absolute reduction in cardiac output is absent in many instances of heart failure.[8–10] Reduction of cardiac output relative to metabolic needs leads to decline in tissue oxygen tension. If such a decline is responsible for sodium retention as has been suggested,[6] one would expect edema to occur during states of severe arterial anoxia. Such is not the case, as most individuals with congenital heart disease or advanced pulmonary fibrosis display no edema despite extreme reduction of arterial saturation. (Calculations of venous oxygen tension in such cases, even allowing for high levels of cardiac output and displacement of the oxygen dissociation curve, indicate values at least as low as those calculated for patients with heart failure.) Furthermore, recent investigations[11] indicate that anoxic anoxia increases sodium excretion.

(2) Under certain conditions heart failure may occur despite high levels of cardiac output, both absolute and relative to metabolic needs.[12]

(3) Marked reduction in glomerular filtration due to intrinsic renal disease is often unassociated with edema. (This objection appears to be valid in regard to the concept of reduced glomerular filtration as the cause of sodium retention, but is not applicable to the alternate concept of increased tubular reabsorption brought about by unknown mechanisms consequent to decline in cardiac output.)

(4) The administration of digitalis to normal persons causes a decline in cardiac output as

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great as that existing in many patients with congestive failure[13] but does not produce edema.

(5) Clinical experience seems to indicate that mechanisms for maintaining blood volume (which necessarily involve retention of sodium) exist independently of alterations in cardiac output. Thus, in menstruating women and in patients with bleeding hemorrhoids the blood volume may remain at normal levels despite frequent loss of blood in amounts much less than the amount required to produce a measurable decline in cardiac output.[14] If a homeostatic mechanism exists which maintains normal levels of blood volume under such conditions, one might suspect that the same mechanism might be concerned in the alterations of blood volume occurring in patients with heart failure.

These considerations appear to cast doubt on the concept that inadequacy of cardiac output institutes homeostatic mechanisms which lead to increase in extracellular fluid volume. They do not, however, constitute evidence against the presence of a homeostatic mechanism brought into play by some stimulus other than inadequacy of cardiac output. If such a mechanism exists, one might expect it to involve the central nervous system, which is so intimately concerned with homeostasis, and one might expect it to be initiated by some functional alteration which is common to peripheral circulatory failure and heart failure. The question, therefore, arises as to what possible alteration in the nervous system might exist in both of these conditions.

Peripheral circulatory failure probably tends to be associated with loss of blood (and extravascular fluid) from the head consequent either to an absolute decline in blood volume, or to a distributional shift of blood to a dilated peripheral vascular bed. Heart failure is attended by an initial accumulation of blood in the central portions of the vascular bed (i.e., in the heart, lungs, and great veins).[15, 16] Such a distributional shift in blood will necessarily tend to lead to deficit of blood in the other portions of the vascular bed. If the patient remains in the sitting position because of dyspnea, the tendency toward loss of blood (and extravascular fluid) from the head will presumably be enhanced. It, therefore, seems probable (although not proved) that in their earlier stages both peripheral failure and heart failure are accompanied by a tendency toward deficit of blood within the cranial cavity. If other factors remain constant, loss of blood from the vessels in the cranial cavity will lower the average capillary pressure and will favor reabsorption of extravascular fluid from the tissues in this region.

Thus the possibility is suggested that intracranial deficit of blood and/or extravascular fluid may exist during the initial phases of heart failure and of peripheral failure, and the question arises as to whether such a deficit could be a factor in causing retention of sodium and water by the kidney. Unfortunately, there are no methods of measuring intracranial fluid volumes. It seems likely, although unproved, that the upright position will tend to reduce the volume of blood and/or extravascular fluid in the cranial cavity, and that compression of the neck will tend to have the opposite effect. The experiments to be reported were, therefore, devised in order to study the effects of these procedures on normal subjects.

METHODS

The sodium excretion of healthy young male medical students was compared in the sitting and recumbent postures. Each subject drank 200 ml. of a 0.14 per cent sodium chloride solution every 30 minutes, and urine was collected hourly for three to nine hours. (This concentration was selected because the experiments of Wolf[17] made it seem likely that more constant results would be secured with it than with other solutions.) Each experiment was preceded by an hour of loading, during which time the subjects ingested 400 ml. of the loading solution, the urine excreted during this preliminary hour being discarded.

A given subject was studied in one position (sitting or recumbent) on a given day, and a few days later was studied in the other position.

Experiments dealing with compression of the neck were conducted in the same manner. A blood pressure cuff was wrapped around the sitting subject's neck and inflated to pressures of 15 to 35 mm. Hg in different experiments.

No attempt at preliminary dietary control was made. The subjects did not usually eat on the day of the six-hour experiments, but one small chocolate bar was consumed midway through the nine-hour experiments. The three-hour experiments on com-

pression of the neck were conducted in the early evening, the last meal having been at noon, some five hours previously.

Blood pressures and pulse rates were recorded every 30 minutes.

The temperature of the room in which the experiments were conducted never varied more than 3 C.

Sodium was measured by a slight modification of the technic described by Hoffman and Osgood.[18]

The modifications were as follows:

1. Protein was removed by the addition of 1 ml. of a 20 per cent trichloracetic acid solution to 5 ml. of urine and filtering through a Whatman No. 42 ashless filter.

2. Either 0.5 ml. or 1.0 ml. of the above filtrate was then added to 10 ml. of recently filtered uranyl zinc acetate solution and the mixture stirred vigorously for two minutes.

3. Only one ether washing was performed.

4. To the completely washed precipitate 11 ml. of triple distilled water were added and the tubes inverted until solution had occurred. The solution was recentrifuged at 1200 revolutions per minute for 10 minutes.

5. The solution was carefully decanted into colorimeter tubes, which were placed in a water bath held at a temperature of 34 C. for 20 minutes. The tubes were then placed in the Evelyn photoelectric colorimeter and read, using a 520 filter.

6. Instead of reading the solutions against a blank of distilled water, a blank of triple distilled water was carried through each procedure and the readings made against it.

Results

1. *The Effect of Variations in Posture on the Excretion of Water and of Sodium.* The data for normal subjects are summarized in table 1.

In both the sitting and the recumbent positions the *urine volume* increased shortly after the subject began to drink the dilute solution of sodium chloride. Diuresis began within the first hour but did not attain a peak until several hours had passed. These findings, when considered in relation to those of Verney,[20] are compatible with the assumption that the increase in urine volume was mediated by inhibition of the antidiuretic hormone of the posterior pituitary, presumably consequent to the ingestion of hypotonic solutions.

The findings of others[17, 19] were confirmed, for the urine volume usually was greater in the recumbent than in the sitting position.

Sodium excretion was greater in the recumbent position in seven of eight comparisons, a minimal change in the reverse direction being encountered once.* The degree of change in sodium excretion with posture tended to be somewhat greater than that in urine volume in most instances, but this finding was inconsistent.

The time factor appeared to be of importance. Thus, although the expected individual variation was encountered, the average values indicated a decreased excretion of sodium in the sitting position of about 30 per cent during the first hour, and of about 50 per cent during subsequent hours (table 1). The delay in onset of the maximal effect suggests the possibility that a chemical mechanism of some type may be set off by changes in posture.

2. *The Effect of Compression of the Neck on the Excretion of Water and of Sodium in the Sitting Position.* The data are summarized in table 2.

The changes in *urine volume* were variable and no general trend was observed. In several instances the urine volume decreased sharply during a period of headache induced by the application of a pressure of 35 mm. Hg. Headache occurring spontaneously in a migrainous subject was also found to decrease urine volume. Since it has been shown[20] that emotions cause release of antidiuretic hormone from the posterior pituitary, this observation is not surprising.

When the pressure in the cuff was 35 mm. Hg, the *sodium excretion* increased in seven of eight comparisons. Since this pressure produced considerable discomfort, investigations were made at lower levels of compression.† Fifteen mm. of pressure produced no discomfort, but led to little or no increase in sodium excretion during a period of three hours. On the other

* The apparent discrepancy between these results and those of Kattus and associates[7] is readily explained. Those investigators found no alteration in sodium excretion on changing from the recumbent to the sitting position. Our observations suggest that the lag in the effect is greater than the duration of the period (20 minutes) during which their subjects were studied in the sitting posture.

† Because of the thickness of the intervening tissues, it is uncertain what fraction of the pressure in the cuff was transmitted to the internal jugular vein.

TABLE 1.—*Urinary Excretion of Sodium and of Water of Normal Subjects in Recumbent and Sitting Postures*

Subject	Duration of experiment in hours	Fluid Ingested		Recumbent					Sitting				
		Composition % NaCl	Volume ml./hr.		1st hour	2nd hour	3rd hour	Total		1st hour	2nd hour	3rd hour	Total
TT	3	0.14	400	Urine ml.	430	550	400	1380	Urine ml.	285	400	425	1110
				Sodium mg.	170	275	327	772	Sodium mg.	95	147	147	389
DS	3	0.14	400	Urine ml.	500	530	380	1410	Urine ml.	70	560	340	970
				Sodium mg.	390	560	525	1475	Sodium mg.	405	400	345	1150
RP	3	0.14	400	Urine ml.	550	610	520	1680	Urine ml.	510	380	470	1360
				Sodium mg.	315	360	455	1130	Sodium mg.	70	115	180	365
F6	3	0.14	400	Urine ml.	650	750	510	1910	Urine ml.	390	300	340	1030
				Sodium mg.	165	315	370	850	Sodium mg.	115	105	115	335
EB	3	0.14	400	Urine ml.	540	610	400	1550	Urine ml.	430	610	520	1560
				Sodium mg.	225	305	370	930	Sodium mg.	235	250	240	725
BC	3	0.14	400	Urine ml.	70	550	565	1185	Urine ml.	615	440	470	1525
				Sodium mg.	95	150	255	500	Sodium mg.	35	165	230	530
JL	6	0.14	400	Urine ml.	470	542	255	2996	Urine ml.	335	350	240	
					600	691	438			290	50	155	1420
				Sodium mg.	608	535	385	2959	Sodium mg.	438	175	62	1136
					671	475	285			330	70	61	
SMS	6	0.14	400	Urine ml.	239	412	345	2131	Urine ml.	55	196	395	1281
					355	240	540			155	215	265	
				Sodium mg.	311	224	176	1521	Sodium mg.	166	82	122	706
					301	218	291			151	105	80	—

TABLE 2.—*Effect of Compression of the Neck of Sitting Subjects on the Urinary Excretion of Sodium and of Water*

Subject	Length of Experiment, hours	Cuff Pressure, mm. Hg	Fluid Ingested		Sitting Position with Cuff		Sitting Position without Cuff	
			Conc. NaCl %	Volume, ml./hr	Total Urine Volume, ml.	Total Sodium, mg.	Total Urine Volume, ml.	Total Sodium, mg.
RP	3	35	0.14	400	1123	809	1357	368
TT	3	35	0.14	400	635	556	1110	390
DS	3	35	0.14	400	1509	1542	972	1156
FG	3	35	0.14	400	1232	450	1029	340
EB	3	35	0.14	400	1390	524	1553	723
BC	3	35	0.14	400	623	620	1529	534
SMS_4	6	35	0.14	400	2287	1698	1294	687
JL	6	35	0.14	400	2180	1515	1920	1143
JL	9	20	0.14	400	3469	1201	2609	520
RB	9	20	0.14	400	4272	2468	3231	1035
BC	3	15	0.14	400	1299	780	1529	534
DS	3	15	0.14	400	1323	882	972	1156
RP	3	15	0.14	400	828	668	1357	368
ZS	3	15	0.14	400	1219	484	1239	902
BJ	3	15	0.14	400	1411	1273	1350	1157
TG	3	15	0.14	400	114	318	711	447
VK	3	15	0.14	400	1132	601	1202	439

hand, pressures of 20 mm. were tolerated readily, and produced well marked increase in sodium excretion during nine-hour experiments.

Measurements of pulse rate and of blood pressure yielded no significant changes when the neck was compressed. It is, therefore, unlikely that the carotid sinus mechanism was concerned in the changes in sodium excretion.

Discussion

The starting point of these studies was the idea that certain alterations in the distribution of body fluids might be reflected in changes in sodium excretion. The data which have been presented are compatible with this concept. As compared to recumbency, the sitting position caused decline in sodium excretion. This decline could be partially prevented by compression of the neck of sitting subjects. These findings could be interpreted as suggesting the existence within the cranial cavity of a volume regulating mechanism. However, the data are deficient in certain respects: sodium intake was not standardized prior to the experimental periods, and it would be desirable to know whether elimination of the variable would result in more uniform results. The effects of compression of the neck were studied only in the sitting position, and it is uncertain whether this procedure would influence the sodium output of recumbent subjects.

Likewise, it is not clear from the data whether the degree of cervical compression of the neck required to induce changes in sodium excretion is within or without the range of venous congestion occurring in health and in disease. For these reasons, and others which will be discussed in subsequent communications, it would seem desirable to defer interpretation of the results until additional studies have been completed. Such studies are in progress and will be reported in a subsequent communication.

Summary

1. Healthy young men ingesting hypotonic sodium chloride solution displayed a well marked decline in the excretion of water and of sodium in the sitting as compared to the recumbent position.

2. This effect of the sitting posture on sodium excretion could be partially but not entirely overcome by compression of the neck.

3. Further investigations are needed in order to determine whether the observations are pertinent to the mechanisms controlling sodium excretion in health and in disease.

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Experimental and Clinical Evaluation in Man of Hexamethonium (C6), A New Ganglionic Blocking Agent

By FRANK A. FINNERTY, JR., M.D., AND EDWARD D. FREIS, M.D.

In man, C6, a new ganglionic blocking agent (50 mg. intravenously) produced inhibition of the Valsalva, tiltback and cold pressor vasopressor responses. Marked increases in digital blood flow and skin temperature with inhibition of digital reflexes to "noxious" stimuli were consistently observed (room temperature 70 F.). The increase in skin temperature was greater and more lasting than following Priscoline or tetraethylammonium chloride. Except for severe postural hypotension, side effects were minimal. Clinically the drug may be useful in the evaluation of sympathetic vasoconstriction in peripheral vascular disease as well as in the treatment of acute neurogenic vasospasm.

THE SUBSTANCES which inhibit transmission of sympathetic vasoconstrictor impulses may be divided into three main categories: (1) central blocking agents which interfere with sympathetic vasoconstrictor reflexes (cardioaortic, carotid sinus) through a central nervous system site of action, such as plasmochin[1] pentaquine[2] and the central blocking component of the DH alkaloids of ergot[3]; (2) adrenergic blocking agents which interrupt sympathetic nerve impulses peripherally and which also block or reverse the effects of injected epinephrine or norepinephrine, such as Dibenamine[4] and Priscoline[5]; and (3) ganglionic blocking agents of which tetraethylammonium chloride (Etamon) is the best known example. The blocking agents inhibit transmission through all autonomic ganglia including the parasympathetic as well as the sympathetic.[6] In addition, they enhance rather than block the pressor effects of epinephrine and norepinephrine in both man[7] and animals.[8]

Paton and Zaimis[9] recently have introduced a series of polymethylene bistrimethyl ammonium salts with interesting properties; the decane derivatives (C10) exhibit curariform activity while the pentane (C5) and hexane (C6) derivatives exhibit ganglionic blocking action. The latter agents appeared to be five times as potent as tetraethylammonium salts. Studies in man by Arnold and his co-workers using C5[10] and by Burt and Graham using C5 and C6[11] suggest that these drugs produce a more complete and lasting ganglionic blockade with fewer side effects than any other agent used thus far. The purpose of the present report is to confirm and extend the observations of these British investigators on the effects of C6 in man.

MATERIALS AND METHODS

The subjects were ward and private patients at Georgetown University Hospital, the Veterans Administration Hospital and Gallinger Municipal Hospital, Washington, D. C. Fifty-five patients were studied. Many were considered normal subjects insofar as their cardiovascular system was concerned while others were suffering from various types of peripheral vascular disease or from hypertension. The drug was given intravenously in dosages of 20 to 100 mg. of active substance dissolved in a sterile solution of either isotonic benzyl alcohol or saline. It was also given intramuscularly in doses of 40 to 60 mg.

For the hemodynamic studies of the vasopressor responses following the Valsalva maneuver, quick tiltback, and immersion of the hand in icewater, an 18 gage needle was inserted into the brachial artery through novocainized skin. This was connected to a three-way stopcock which in turn was connected to a Sanborn electromanometer. Heparin solution

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was flushed through the stopcock intermittently to insure patency. All tests were carried out in a quiet room with the patient lying on a tilt-table.

Skin temperature was measured using iron-constantan wire thermocouples taped lightly to both big toes, both index fingers, umbilicus, right forearm, right upper arm and right shoulder. Two additional thermocouples were used for recording room temperature. A graphic chart of all of these ten points was automatically recorded every five minutes on a Leeds-Northrup series G "Speedomax" equipped with a multiple point recorder. This method of registration permits continuous and automatic charting of skin temperature changes without disturbance to the patient by the examiner. Room temperature varied no more than 2 degrees F. in any experiment but testing was carried out in both cool (68 to 72 F.), moderate (74 to 78 F.) and warm (78 to 86 F.) environmental temperatures in different experiments. The patient reclined semiclothed on a comfortable bed. In all instances skin temperatures reached an equilibrium and remained constant for at least 30 minutes prior to the administration of the drug. The period of observation after the drug was at least one hour.

Digital plethysmography was carried out using the Burch-Winsor plethysmograph[12] simultaneously with skin temperature measurements. A digital pneumatic cuff was used for venous congestion of the digits at a congesting pressure of 50 mm. Hg. Blood flow was determined according to the method of Robertson, Farmer and Smithwick.[13]

Results

Inhibition of Sympathetic Vasoconstrictor Responses

Certain vasopressor responses, usually diminished or abolished following surgical sympathectomy, were completely blocked or definitely inhibited after 50 mg. of C6 administered intravenously. These included:

A. Valsalva Vasopressor Overshoot. After intravenous administration of C6, the normal vasopressor overshoot of arterial pressure following the Valsalva maneuver[14] was abolished in 4 out of 5 patients, and markedly inhibited in the other (fig. 1). The effect appeared in 1 to 2 minutes following injection and lasted 30 to 60 minutes or longer.

B. Cold Pressor Response. The cold pressor response was completely blocked in 6 and markedly inhibited in 2 of the 8 patients tested as compared with the hypertensive response before administration of C6 (fig. 2).

C. Postural Hypotension. All subjects developed a marked fall in arterial pressure in the upright position, frequently to collapse levels. In addition, the usual vasopressor overshoot[14] which occurs on tilting back quickly from the erect to the supine position was abolished.

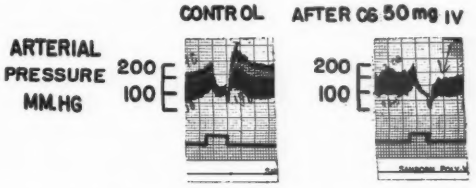

FIG. 1. Chart of arterial pressure illustrating the abolition of the vasopressor "overshoot" following Valsalva maneuver in patient E. M., a 30 year old Negro woman with essential hypertension. See text for method of recording. Paper speed was 0.5 mm. per second. The elevation of the lower line indicates the 10-second period during which the patient blew out forcibly into a closed tube. During the control period following release of the expiratory effort a momentary elevation of both systolic and diastolic pressure occurred above the basal level. After C6 this "overshoot" was abolished.

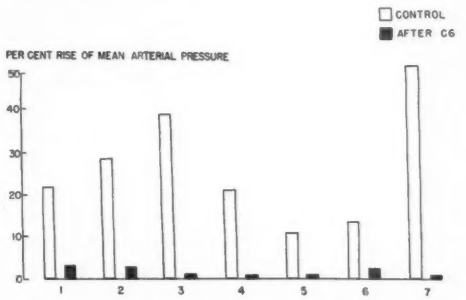

FIG. 2. Chart of the cold pressor responses before and after C6 in 7 hypertensive patients. Prior to the drug the per cent rise in mean $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ arterial pressure on immersion of the hand in ice water varied between 10 and 52 per cent. Following the drug the rise in mean arterial pressure varied between 0 and 4 per cent.

D. Congestion Collapse. It has been demonstrated previously that after sodium nitrite or certain drugs which inhibit sympathetic vasoconstrictor reflexes collapse will occur in the supine position following venous congestion of the limbs.[15] This procedure was carried out by placing blood pressure cuffs proximally on both thighs and one upper arm and inflating them to pressures slightly below diastolic blood pres-

sure. Following C6 in all of 4 subjects examined a marked fall in arterial pressure with collapse occurred within three minutes after congesting the limbs, whereas prior to the drug, similar congestion of the limbs for a period of five minutes produced insignificant changes in arterial pressure in the same subjects.

Arterial Pressure, Supine

The effect of C6 on arterial pressure and pulse rate in the recumbent position was determined in 10 normotensive and 18 hypertensive patients. In the normotensive group, there was a mean fall in systolic arterial pressure of 10 per cent (range 4 to 18 per cent) and a mean fall in diastolic pressure of 7 per cent (range 0 to 20 per cent). The decrease in arterial pressure began almost immediately following injection and lasted one-half to one hour. An increase in heart rate averaging 21 beats per minute developed 1 to 2 minutes after injection and lasted 20 to 40 minutes.

In the hypertensive group the mean reduction in systolic pressure was 34 per cent with a range of 12 to 63 per cent. The average fall in diastolic pressure was 22 per cent (range 3 to 50 per cent). Thus, the reduction of both systolic and diastolic pressure was much greater in the hypertensive than in the normotensive patients. Two hypertensive patients who exhibited reductions of mean arterial pressure of 52 and 53 per cent respectively developed faintness and nausea. These symptoms and the extreme hypotension were relieved by tilting the bed into a head-down position.

Skin Temperature and Digital Blood Flow

The most marked and consistent effects of C6 were observed in the digits (fig. 3). Unlike the results obtained following dihydroergocornine[16] the percentage rise of digital skin temperature following C6 was greater in cool than in warm environments. Observations were made in 22 patients. Nine patients were studied in cool environments (66 to 72 F.). Following C6 in this group there was a mean rise of toe temperatures of 17 F. and an increase in finger temperatures of 11 F. Seven patients were studied in moderate environments (72 to 80 F.); in this group the average rise in toe temperatures following C6 was 9.3 F. In warm environments (80.5 to 86.5 F.) the average increase in toe temperatures in 6 patients was 6.6 F. and in finger temperatures was 3.0 F. In all cases except those who had organic obstruction of the larger arteries the temperature gradient between the toe and umbilical temperature was abolished, this response occurring in the cool as well as in the warm room.

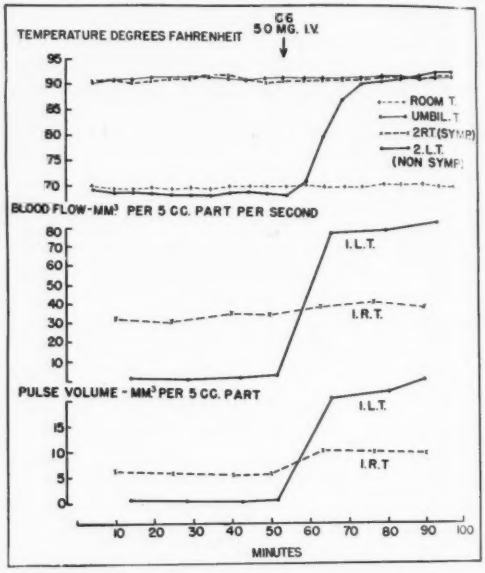

FIG. 3. Chart illustrating the effects of C6 on toe temperature, blood flow and pulse volume in patient F. A., a 28 year old woman, whose right lower extremity had been sympathectomized one year previously because of postphlebitic pain and edema. The room was maintained at a constant temperature of 70 F. throughout the experiment. In the right lower or sympathectomized extremity skin temperature recorded from the second toe was approximately 91 degrees and equalled the umbilical temperature. In the left lower (unsympathectomized) extremity the toes were cold. However, following C6 the toe temperature on the unsympathectomized side rose from 68 to 92 F. with abolition of the skin temperature gradient. The rise in blood flow and pulse volume on the unsympathectomized side paralleled the change in skin temperature. In the sympathectomized extremity there was a slight rise in blood flow and pulse volume probably indicating that the sympathectomy had not been quite complete.

As noted previously by Burt and Graham[11] the rise in toe temperature usually was of greater degree and of longer duration than the elevation in finger temperature. Occasionally, however, the rise in finger temperature approximated the toe temperature and in 2 subjects who had an exceptionally marked vasoconstrictor response in the fingers to cold, the elevation of finger temperature exceeded that in the toes by 10 and 12 F. respectively.

The rise in digital skin temperature began in 2 to 10 minutes after intravenous injection, reached a peak in 15 to 30 minutes and then gradually subsided to pre-injection levels over a period of 2 to 6 hours. Patients often experienced a feeling of warmth in the toes and absence of sweating of the feet which sometimes persisted for as long as 6 hours.

In contrast to the poor correlation observed in subjects in warm rooms it is generally recognized that changes in digital skin temperature usually reflect changes in digital blood flow when the subject is examined in a cool room.[12] Nevertheless, plethysmographic measurements of digital blood flow were carried out in 6 subjects before and after the intravenous injection of 50 mg. of C6. In all cases the digital blood flow doubled and in some instances rose much higher (fig. 3). In addition, there was a marked increase in pulse volume (fig. 4) and inhibition or abolition of the vasoconstrictor response to "noxious" stimuli such as a deep breath and ice applied to the face. The increase in pulse volume and blood flow usually was greater and of longer duration in the toes than in the fingers.

Comparison with TEA and Priscoline

The marked and consistent effects of C6 on digital blood flow especially in the toes suggested that a promising clinical application of the drug might be in the field of peripheral vascular disease. It seemed advisable, therefore, to compare C6 with other agents used clinically in the diagnosis and treatment of peripheral vasospastic disorders. The response of digital skin temperature in a cool environment was used as the basis of comparison. Patients were given different drugs on consecutive days, the room temperature being maintained at the same level each day.

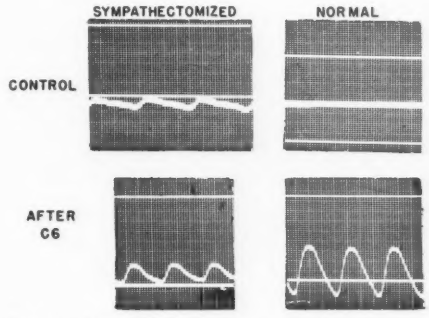

FIG. 4. Chart showing cuttings taken from the plethysmographic record of patient F. A. (fig. 3). On the sympathectomized side there was a moderate increase in pulse volume in the toe after C6. In the unsympathectomized or normal limb prior to C6 there are no perceptible pulse waves due to the marked vasoconstriction in the cool room. However, after C6 there was a marked increase in pulse volume.

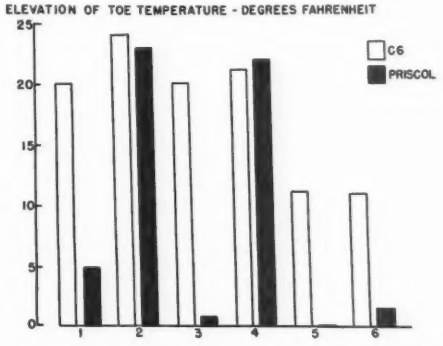

FIG. 5. Chart showing elevation of toe temperature in 6 patients given either Priscoline 50 mg. intravenously or C6, 50 mg. intravenously, on alternate days. Room temperature was maintained at the same level each day (70 degrees F. in most experiments). In cases 2 and 4 the rise in toe temperature following Priscoline equalled that following C6 but in the other 4 patients the elevation of toe temperature following C6 was significantly greater than that following Priscoline.

Six patients were given 50 mg. of Priscoline intravenously (fig. 5). Following intravenous Priscoline the duration of the rise in skin temperature was somewhat shorter than the temperature rise following C6. In all cases the in-

jection was followed by parasthesias, palpitation, flushing of the skin, nasal stuffiness and in 4 instances by shivering. The rise of digital skin temperature in this cool environment was significant in some patients and insignificant or absent in others. In cases 1 and 3 (fig. 5), the rise in toe temperature following C6 exceeded that following Priscoline by 15 and 20 F. respectively, in case 5 by 12 F. and in case 6 by 9 F. In cases 2 and 4 the rise in toe temperature after Priscoline equalled that following the injection of C6 but in these 2 cases the rise in finger temperatures was 11 and 13 degrees greater respectively following C6. In

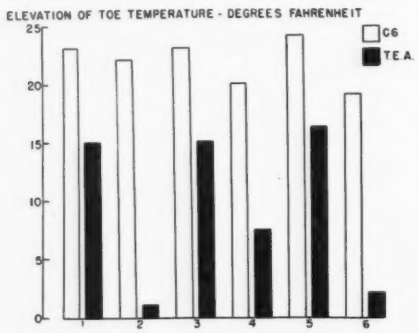

FIG. 6. Chart showing elevation of toe temperature in 6 patients given either tetraethylammonium chloride, 400 mg. intravenously, or, C6, 50 mg. intravenously, on alternate days. Experimental conditions similar to those described for figure 5. In every case the elevation of toe temperature following C6 was significantly greater than that following TEA.

another patient with far advanced arteriosclerosis obliterans of the left leg, neither C6, intravenous or intraarterial Priscoline nor lumbar paravertebral block induced with procaine resulted in any significant rise in the temperature of the toes.

Similar comparisons were made between the effects of 50 mg. of C6 given intravenously as compared to 400 mg. of tetraethylammonium given by the same route. In all of the 6 patients studied a significantly greater rise in digital skin temperature occurred following C6 as compared to TEA (fig. 6). In cases 2 and 6 (fig. 6), the rise in the toe temperature after the drug exceeded that following TEA by 20 and 18 F. respectively. In cases 1 and 3 the increase was 8 degrees greater, in case 4 it was 14 degrees and in case 5 the rise in toe temperature was 7 degrees higher following C6 than that observed after TEA. The rise in digital skin temperature following TEA was fleeting in character, lasting only 15 to 20 minutes, as compared with a duration of at least one hour following C6. Accompanying the injection of TEA all of the 6 patients studied complained of unpleasant paresthesias, a metallic taste and palpitation. These side effects were not noted after the administration of C6.

Site of Action

Paiton and Zaimis[9] demonstrated in animals that C6 produces its effects by blocking transmission through all autonomic ganglia. Positive proof of ganglionic inhibition cannot be determined readily in man. However, a similar site of action in the human is strongly suggested by the following observations: (1) the injection of small doses (12 mg.) of Priscoline intraarterially in 3 subjects resulted in a significant elevation of skin temperature in the injected limb as compared with the contralateral limb. However, intraarterial injection of 10 to 20 mg. of C6 in the same subjects resulted in no significant increase in the skin temperature of the injected limb. Thus, C6 appeared to have no peripheral vasodilating action in man. (2) True ganglionic blocking agents paralyze transmission of impulses through all autonomic ganglia including the parasympathetic as well as the sympathetic. Therefore, following C6 the parasympathetic or vagal influence on the heart should be abolished so that subsequent injection of atropine would be without effect on cardiac rate. Three patients were given 60 mg. of C6 intravenously following which the heart rate increased by 20 to 30 beats per minute. After attaining a steady state an atropinizing dose (1 mg. of atropine sulfate) was injected intravenously following which in no instance was there any further change in heart rate. (3) In contrast to drugs which inhibit transmission of sympathetic nerve impulses at other sites the ganglionic blocking agents increase the pressor effects of

epinephrine and norepinephrine.[7] In 3 normal subjects epinephrine (1 μg. per cc.) and norepinephrine (1.5 μg. per cc.) were given alternately by continuous intravenous infusion. Following C6 the same doses of epinephrine and norepinephrine produced significantly greater rises in arterial pressure after as compared to before the drug. These various observations strongly suggest that the site of action of C6 is at the autonomic ganglia in man as well as in animals.

Dosage and Routes of Administration

During the early phases of this investigation doses of 20 to 30 mg. were given intravenously, but at this dosage the abolition of sympathetic reflexes was inconstant. Hence, the dosage was raised to 50 mg. Intravenous doses as high as 100 mg. have been given but these seemed to be no more effective than the 50 mg. dose. The drug was also active in 50 mg. doses following intramuscular injection. However, oral and sublingual doses as high as 500 mg. were completely inactive. Thus, it would appear that for diagnostic studies or other instances in which a rapid effect is desired an intravenous dose of 50 mg. is well tolerated and effective, whereas for continuous administration the drug may be given intramuscularly in similar dosage at intervals of 3 to 4 hours.

Side Effects and Tolerance

Except for the development of severe postural hypotension the side effects following C6 were few and of minor consequence. Most patients noted no subjective sensations. Slight dilatation of the pupils frequently occurred and 12 patients complained of blurred vision which usually persisted no longer than 10 minutes. A few patients noted a dry mouth; 6 patients complained of drowsiness and 3 of transient nausea. However, there were no instances of vomiting, paresthesias, flushing, nasal stuffiness or palpitation.

The more complete the ganglionic blockade the more readily will postural collapse result. Following C6 postural hypotension persisted for as long as two hours in some patients. In a few cases tested in the supine position it was necessary to elevate the foot of the bed slightly in order to combat a steady fall in arterial pressure. C6 has been reported to produce collapse in anesthetized individuals[17] and probably should never be used in patients who have suffered recent blood loss since the drug effectively blocks compensatory vasoconstrictor mechanisms.[15] In 2 patients with hypertension, coronary artery disease and angina pectoris a marked fall in arterial pressure in the supine position precipitated a bout of angina. Both the hypotension and the angina were relieved by elevating and passively exercising the lower extremities.

Although studies of the effect of continued treatment with C6 are still in the preliminary stages, observations in 2 patients who were given daily injections of the drug did not indicate the development of any significant degree of tolerance. For example, in a patient with thrombophlebitis 50 mg. of C6 was administered daily for eight days. On the eighth day a rise of toe temperature of 17 F. following the drug was as great as the rise following the first injection. In a similar patient 30 mg. of C6 was administered daily for four days and every other day for six days with no evidence of development of tolerance to the drug. It has not yet been determined whether tolerance develops when the drug is administered at more frequent intervals.

Discussion

As a ganglionic blocking agent C6 differed from tetraethylammonium, the prototype of such drugs, in several important respects: (1) C6 appeared to be more potent than TEA in man since 50 mg. doses appeared to produce maximal effects. (2) The duration of action of the drug was approximately five time longer than TEA, the effects of C6 lasting 1 to 2 hours as compared with 15 to 20 minutes in the case of TEA. (3) The injection of C6 was not attended by the disturbing and unpleasant side effects of TEA such as metallic taste, generalized tingling and other paresthesias.

The most striking vasomotor effect of the drug was the marked elevation of skin temperature and blood flow in the digits, partic-

ularly in the toes. In evaluating sympathetic blocking agents it is important that the skin temperature measurements be carried out in a cool although not excessively cold environment. First, digital skin temperature and blood flow changes parallel each other only under such conditions[12]; and, second, sympathetic vasoconstrictor nerves to the digits are activated in cool rather than in warm environments. In fact, a hot environment may effectively abolish vasoconstrictor tone.[18] The importance of controlling room temperature was demonstrated in studies with dihydroergocornine,[16] where it was found that the drug produced a rise in digital skin temperature in warm but not in cool environments. Similarly, Priscoline will abolish the temperature gradient between the toes and the umbilicus at environmental temperatures of 77 F.[5] but, as shown in these studies, will not do so uniformly at room temperatures of 68 to 72 F.

As suggested by Burt and Graham[11] the reason that C6 usually produced a greater rise of skin temperature in the toes as compared with the fingers might be due to the greater inherent vasoconstrictor tone in the lower limbs.[18] This explanation is supported by the observation that in 2 patients with abnormally cold hands the rise in finger temperature exceeded that in the toes. The regular occurrence of a marked rise in toe temperature in a cool room following C6 suggests that sympathetic vasoconstrictor impulses to this area were markedly inhibited if not completely abolished. Studies are in progress to determine the extent of sympathetic block using as an index the increase in blood flow in the foot after C6 as compared with the effects of lumbar paravertebral block.[19]

The failure of TEA to bring about a comparable rise in skin temperature may be related more to the short duration of action of the drug rather than to its lack of potency. The skin temperature changes following C6 occurred slowly, maximum values being attained after 10 to 30 minutes. Since the duration of action of TEA is brief it is possible that the ganglionic inhibition produced by this drug was wearing off before maximum skin temperature changes could occur.

Because of the drug's potent effect on digital blood flow and skin temperature C6 may be useful in the evaluation of patients with peripheral vascular disease. In such cases the intravenous injection of C6 may provide a rapid and simple method of assessing the role of the sympathetic vasoconstrictor mechanisms without discomfort to the patient. For example, in a case of causalgia of the right hand following an old injury to the wrist C6 effectively relieved the pain and hyperesthesia for several hours. Sympathectomy was performed subsequently with complete relief of pain. In another patient with Raynaud's phenomenon characteristic color changes developed in the fingers whenever the hands were placed in cold water. This cold-induced attack was completely, although only temporarily, blocked following the injection of C6.

The drug also may be useful in the treatment of acute peripheral vascular disorders such as acute thrombophlebitis, or thrombosis or embolism of peripheral arteries whenever it is desirable to abolish the effects of reflex vasospasm. In the present study 3 cases of acute thrombophlebitis have been treated with daily injections of 50 mg. of C6. As judged by relief of pain and improvement in color and temperature of the involved foot the results seemed comparable to those usually obtained with lumbar paravertebral block induced with procaine. However, evaluation of these suggested clinical applications of C6 must await extensive studies in a large series of patients.

Summary and Conclusions

Hexamethonium (C6), a new ganglionic blocking agent, was administered in doses of 50 mg. intravenously to a heterogeneous group of 55 individuals including normal subjects and patients with various diseases of the vascular system with the following results:

1. Sympathetic vasopressor reflexes including the hypertensive overshoot to the Valsalva maneuver and the tiltback overshoot were inhibited or abolished. The cold pressor response was markedly inhibited, as were the reflex vasoconstrictor responses in the digits to "noxious" stimuli.

2. A significant increase in digital skin tem-

perature, usually with abolition of the temperature gradient, occurred in cool as well as in warm environments. The response was more marked in the toes than in the fingers except when the latter exhibited abnormal vasoconstriction. The rise in digital skin temperature was accompanied by simultaneous increases in digital blood flow and pulse volume as measured plethysmographically.

3. In the same subjects studies in comparable environmental temperatures (room temperature approximately 70 F. and stationary) the rise in digital skin temperature after C6 was usually greater and more prolonged than that achieved following either Priscoline (50 mg. intravenously) or tetraethylammonium (400 mg.).

4. The reduction in supine arterial pressure frequently was minimal in normotensive subjects while, although variable in degree, it was sometimes marked in hypertensive patients. Because of the inhibition of sympathetic vasoconstriction, a severe postural hypotension was a regular occurrence. For this reason the drug may precipitate vasomotor collapse in the erect or sitting position or after moderate degrees of blood loss. Occasional severe hypotensive reactions occurring in the supine position could be prevented or treated by slightly elevating the foot of the bed.

5. When injected intravenously the duration of action of the drug was 1 to 2 hours. C6 was effective by all routes of parenteral administration but was inactive after oral or sublingual administration.

6. Adverse subjective sensations such as paresthesias, palpitation, flushing, nausea, were completely absent. However, postural hypotension was severe and 2 patients with angina pectoris developed anginal attacks during severe hypotensive reactions.

Preliminary data suggest that the drug may be used clinically in the evaluation of the sympathetic vasoconstrictor component in cases of peripheral vascular disease as well as in the treatment of acute peripheral vascular disorders associated with neurogenic vasospasm.

ACKNOWLEDGMENT

The authors wish to thank Messrs. Raymond E. Flath and Henry G. Gillem for valuable technical assistance.

ADDENDUM

Since preparation of this paper, Turner (Lancet **2:** 353, 1950) has reported that doses of 1.5 to 5 Gm. of hexamethonium bromide are effective by the oral route of administration. Thus it would appear that the effective oral dose is approximately 50 to 100 times greater than the effective parenteral dose.

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The Subcutaneous Use of Heparin

A Summary of Observations

By GEZA DE TAKATS, M.D.

The present use of anticoagulants is hampered by the necessity of giving a number of injections of heparin each day, or of using an oral anticoagulant which acts by throttling prothrombin delivery from the liver and does not seem to be a safe anticoagulant, since its laboratory control is not standardized. Because of this an attempt is made in this paper to show the effectiveness of administering heparin subcutaneously and of giving only enough to restore the clotting mechanism to its normal level but not necessarily prolonging the clotting time. With this principle a single injection of heparin a day or every second day seems sufficient, and the danger of hemorrhage is greatly minized.

BECAUSE there is a definite need for an anticoagulant which need not be injected intravenously, and because of our conviction that dicumarol prophylaxis and therapy are at present unsafe and unpredictable,[1] an investigation of various heparin solutions and suspensions was undertaken with regard to their injectability and efficacy through a deep subcutaneous route. When the site of so-called intramuscular injections—as given by the nursing staff—is examined by biopsy, it is often found to be the deep subcutaneous tissue. The samples tested were 200 mg. of heparin in gelatin,* with and without vasoconstrictors, 400 mg. of heparin in gelatin with and without vasoconstrictors, 200 mg. of heparin in gelatin with, and 200 mg. of depo-heparin without vasoconstrictors and 10 per cent heparin in aqueous solution in doses of 100 and 200 mg.

GENERAL CONSIDERATIONS

While in the case of penicillin the infecting organism is the dominating factor determining penicillin resistance or penicillin sensitivity, in the case of heparin, there is a multiplicity of factors influencing its action. These have been summarized in table 1. In addition, there may be a *daily* change in heparin requirement, and there also seems to be a cumulative action, or possibly a phenomenon of storage.[2] All this indicates the difficulty in prescribing set dosages, and the necessity of utilizing a test dose of heparin (10 mg. in 1 cc. solution given intravenously) before heparin therapy is started.[3] The effect of this dose on the individual is tested by capillary coagulation times, determined before and 10 minutes after the injection. Such tests reveal nonreactors, hyporeactors, mean reactors and hyperreactors. Of 97 normal individuals tested a few years ago, 40 were hyporeactors, 31 were hyperreactors and 20 were mean reactors.[1] In 250 patients there was a much higher percentage of hyporeactors, and nonreactors appeared. The guiding influence of such a test dose on prophylactic and therapeutic dosage is obvious.

Heparin activity can be controlled by coagulation times, and for years we have employed capillary coagulation times for this purpose because (1) this is a simple bedside test, and can be performed by technicians, internes, nurses and even patients; (2) repeated venipunctures in patients under heparin therapy produce hematomata; (3) coagulation times with the one tube Lee-White method may be prolonged from 40 to 60 minutes during therapy with heparin, producing a time consuming procedure; (4) three and five tube Lee-White coagulation times may start with a 25 to 30

From the Fourth Surgical Service, St. Luke's Hospital, Chicago, aided by a grant from the Upjohn Company, Kalamazoo, Michigan.

* This cartridge of Depo-heparin sodium, 200 mg., with vasoconstrictors contains: heparin sodium (20,000 units), 200 mg.; epinephrine hydrochloride 1 mg.; ephedrine hydrochloride, 10 mg.; gelatin, 180 mg.; dextrose, 80 mg. Preserved with sodium ethyl mercuri thiosalicylate 1:10,000.

minute normal coagulation time[4] and silicone-coated tubes may exhibit a 60 to 70 minute normal coagulation time,[5] indicating that all these methods are pure artefacts and that the blood surrounded by a nonwettable endothelial lining does not clot anyway.

For these reasons, capillary coagulation times are advocated, not with the idea of studying the patient's clotting mechanism, but merely to follow and control the administration of heparin. Heparin can of course be titrated in whole blood and in plasma with protamine sulfate, but in our opinion this can never become a satisfactory bedside test for the control of heparin administration. Heparin tolerance can also be tested in vitro,[4] although as pointed out by Best and Jaques[5] the clotting time produced with moderate doses of heparin in vivo is considerably greater than that obtained on mixing the same quantity of heparin with the blood in the test tube. The heparin tolerance in the circulating blood measures the state of the clotting mechanism, a dynamic equilibrium of coagulant and anticoagulant factors, and in addition is influenced by excretion, storage and enzymic degradation.[6] This is the reason why single large intravenous doses are wasteful, and a moderately elevated plateau-type of clotting curve is desirable.

TABLE 1.—*Response to Heparin*

Decreased Response	Increased Response
Age	Youth
Acute Thrombosis	Traumatic or Hemorrhagic Shock
Postoperative State	Hepatic Damage
Dehydration	Neostigmine
Hemoconcentration	Sodium Tetrathionate
Polycythemia	Dicumarol
Hyperlipemia	Carinamide
Carcinomatosis	
Digitalis	
Epinephrine	

The addition of minute amounts of heparin (1 to 4 gamma) to a cubic centimeter of blood in vitro reacts with a number of enzymes, co-factors, profactors and accelerators,[7] the sum total of which inhibit or facilitate the action of heparin, but it is most useful in sensitizing the ordinary Lee-White method of venous coagulation time so that small amounts of additional heparin as used in subcutaneous therapy may be detected by lengthening of the clotting time. Our experience with the recently published method of Rosenthal[8] has been most satisfactory, and has gradually led us to adopt the principle that, for prophylactic purposes, the maintenance of a sensitized clotting time at the upper limit of normal is protective. This means the use of far smaller quantities of heparin than have been advocated in the past, amounting for the adult of average weight to 200 mg. of heparin every 48 hours in a retarding medium such as gelatin. The normal sensitized clotting time varies between 20 and 30 minutes, using 4 gamma as a sensitizer. Figures below or above these indicate hypocoagulability or hypercoagulability of the blood. Elsewhere we have reported on the clinical value of such a sensitized clotting time.[9]

METHODS OF STUDY

The patient's age, sex, diagnosis and other conditions known to influence the response to heparin were noted. A heparin tolerance test was run on each individual before the administration of heparin. A coagulation time was determined before and every two hours after the administration of heparin until the pre-injection level of coagulation time was reached. Often capillary coagulation times were determined more frequently until the peak was reached. Untoward effects, such as pain or hematoma at the site of injection, or bleeding elsewhere, were noted.

OBSERVATIONS

(1) *200 Mg. of Depo-Heparin without Vasoconstrictors.* Figure 1 shows a control of this drug by venous coagulation times. Note that the effect is over in about 12 hours and that the peaks are so high as to make the venous coagulation times impractical. Figure 2 shows the control by capillary coagulation times. Thus, case 6 in figure 2 shows a poor response. This patient, Esther O., a heavy set woman with chronic thrombophlebitic edema, showed marked heparin resistance following operation. In contrast, case 3, a young boy who had just recovered from a massive acute thrombophle-

bitis, showed a good response. The same heparin sensitivity is exhibited by case 4, figure 1, a patient with Buerger's disease in a state of remission.

(2) *200 Mg. of Depo-Heparin with Vasoconstrictors.* Figure 3 shows the control with venous coagulation times, whereas figure 4 illustrates the control by capillary coagulation

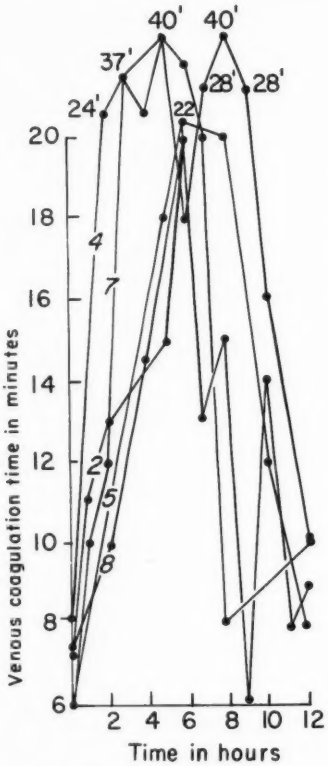

FIG. 1. The effect of 200 mg. of heparin-gelatin without vasoconstrictors on venous coagulation time. Note the high peaks, the steep curves, and the relatively short duration.

times. The highest response in figure 3 is shown by case 10, Bernice O' M., a 30 year old woman with a postphlebitic syndrome. The peak and duration of effect is quite variable. Case 1 of figure 4 is Mary S., a young girl with a congenital vascular anomaly but no thromboembolic disease, who showed a peak of 11 minutes and duration of effect to 30 hours. Case 4 on the other hand is an arteriosclerotic individual of 56, with extensive arterial and venous thrombosis who showed little therapeutic effect; even less did case 6, Charlotte K., who exhibited a postoperative infection. The average duration of effect, which varied from 9 hours to 30 hours, was 22 hours.

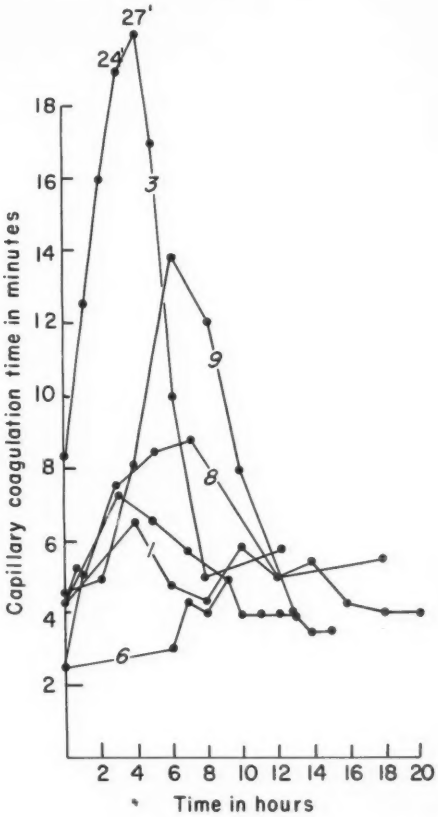

FIG. 2. The effect of 200 mg. of heparin-gelatin without vasoconstrictors on capillary coagulation time. Note the marked variation in response. Case 3 exhibits an exaggerated response in a young boy during the stage of recovery from an acute thrombophlebitis. Case 6 is in a stage of postoperative heparin-resistance.

(3) *400 Mg. of Depo-Heparin without Vasoconstrictors.* Figure 5 illustrates the effect of this dose, measured by capillary coagulation time, and indicates again extreme variability. The high curve with a peak of 32 minutes and a duration of effect up to 38 hours belongs to

Wm. P., a thin, undernourished individual who received with this dose (3.5 mg. of heparin per pound of body weight) an overdose resulting in a large hematoma at the site of injection. On the other hand, curve 3 belongs to Esther

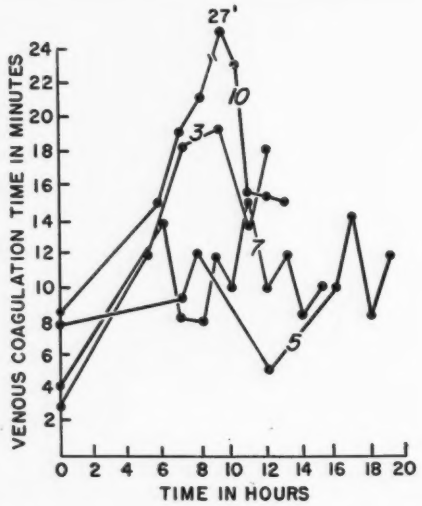

FIG. 3. The effect of 200 mg. of heparin in gelatin with vasoconstrictors, controlled by venous coagulation times. Peak and duration of effect vary markedly.

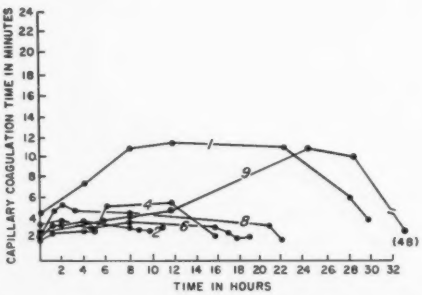

FIG. 4. The effect of 200 mg. of heparin in gelatin with vasoconstrictors on capillary coagulation time. Resistance and sensitivity are demonstrable, but the control is easier because of the shorter clotting times.

O., the same individual who showed poor response to heparin in Figure 3 to 200 mg. of depo-heparin with vasoconstrictors. Her curve dropped to the preinjection level in 12 hours. The duration of effect varied from 19 to 35 hours, with an average of *31 hours*.

(4) *400 Mg. of Depo-Heparin, 200 Mg. with, and 200 Mg. without, Vasoconstrictors.* Figure 6 illustrates the control with capillary coagulation times. These curves are more of a plateau type, show fewer peaks and last from 16 to 32 hours, with an average of 25 hours. Note the almost complete lack of response of

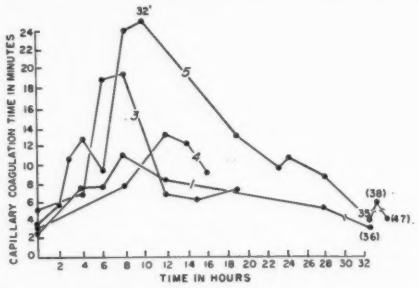

FIG. 5. The effect of 400 mg. of heparin in gelatin without vasoconstrictors on capillary coagulation time. The highest curve (case 5) is the result of an overdose (3.5 mg. of heparin per pound of body weight). The effect lasted 48 hours. In case 3 the effect was not measurable with capillary coagulation times after 12 hours.

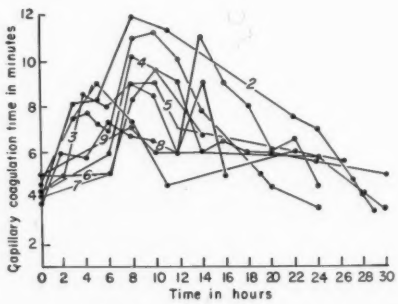

FIG. 6. The effect of 400 mg. of heparin in gelatin with half dose of vasoconstrictors on capillary coagulation time. Case 8 shows minimal response. He was an obese individual, with active arterial and venous thrombosis.

case 8, Henry H., an obese individual with multiple, massive venous and arterial thromboses.

(5) *400 Mg. of Depo-Heparin with Vasoconstrictors.* Figure 7 shows the capillary control. The duration of effect varied from 13 to 48 hours, an average of 27 hours. Noteworthy among the poor responses in the individual

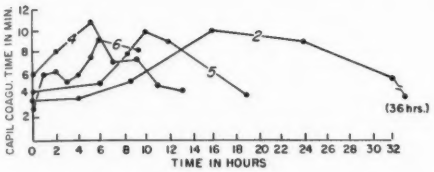

FIG. 7. The effect of 400 mg. of heparin in gelatin with full dose of vasoconstrictors. Capillary coagulation times were used. These are flat curves. Note that in case 2 the effect lasted for 36 hours; in case 5 for 19 hours. Both patients weighed the same, but case 5 had an acute, case 2 a chronic thrombophlebitic edema.

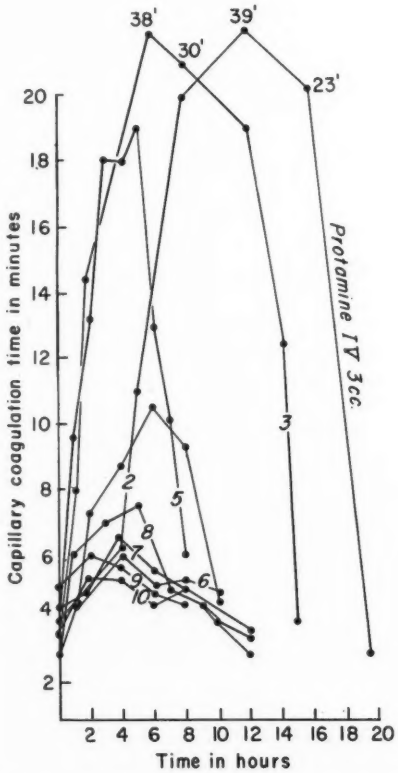

FIG. 8. The effect of 200 mg. of heparin in 10 per cent aqueous solution, given intramuscularly. Capillary coagulation times were used. Note the difference in response between case 2 and case 6. The former received protamine for a severe hemorrhage in an abdominal incision. Case 3 had a subsiding deep thrombophlebitis, with a capillary coagulation time of 38 minutes, at 6 hours, but showed no bleeding.

graphs is that of case 5, Peter G., with an acute thrombophlebitis, who exhibited a poor response, lasting 19 hours.

(6) *150 Mg. of Depo-Heparin with and 150 Mg. of Depo-Heparin without Vasoconstrictors.* Because of our experience with hemorrhagic complications when the 400 mg. dose was ad-

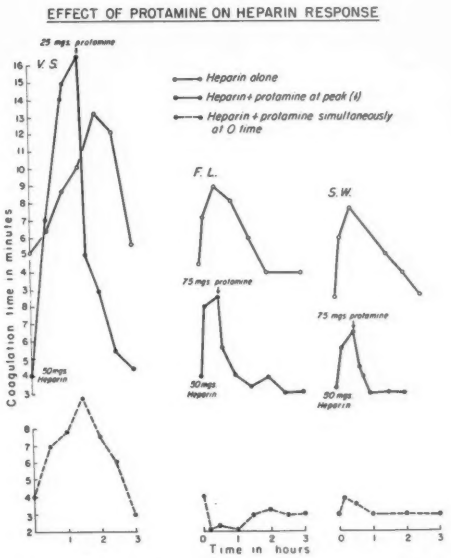

FIG. 9. The effect of intravenous protamine sulfate on the action of heparin. In the left row of curves (V.S.) 50 mg. of heparin were given intravenously, alone; a second time at the peak of response protamine was given; a third time heparin and protamine were given simultaneously. The dose of protamine was one half that of heparin. Note a dampening, but not a neutralizing effect. In the middle row and in the third row, a 1.5 to 1 ratio of protamine to heparin was used. Note that in patients F. L. and S. W., protamine, given at the peak, promptly restored the clotting time to normal; given simultaneously, it completely neutralized the effect of heparin, which showed a good effect in both patients when given alone.

ministered to patients weighing around 120 pounds, this dosage was administered to a few patients. Even this dose resulted in a large postoperative hematoma in Vesta W., who received 1.71 mg. of heparin per pound of body weight. This case will be discussed under the heading of untoward reactions.

(7) *200 Mg. of Heparin in 10 Per Cent Aque-*

ous Solution. There is again a tremendous variation in the effect of this injection. Figure 8 shows the capillary control with high peaks and a duration varying from 7 to 19.5 hours. One case in this group developed a severe hemorrhage. This patient, case 2 of Figure 8, will be discussed in detail. Note the poor response of case 6, J. B., a 44 year old vascular sclerotic, whose capillary coagulation times hardly show a rise.

The Neutralization of Heparin by Protamine Sulfate

Various doses of protamine sulfate were given intravenously to neutralize the action of heparin (fig. 9). While a 1:1 ratio of protamine to heparin definitely dampens the effect of heparin, a complete suppression of the heparin effect on capillary coagulation time is obtained by a 1.5:1 ratio. Thus 75 mg. of protamine sulfate given simultaneously (but not in the same syringe) with 50 mg. of heparin, has led to the flattening of clotting curves.

When protamine sulfate is given at the height of the clotting curve, within 10 minutes there is a steep fall of the clotting time to a lower level.

Here again a 1.5:1 ratio (i.e. 75 mg. of protamine to 50 mg. of heparin) seems the most effective, but smaller doses, such as a 0.5:1 ratio, are partially effective. (fig. 9).

So far, there have been no untoward reactions following the intravenous use of protamine; when given into muscle there is severe burning for 24 hours, but a noticeable antiheparin effect. We do not advise the latter method of administration unless it can be made more painless, possibly with procaine as in the case of aminophylline.

The duration of the effect of intravenous protamine is approximately four hours. Heparin response up to four hours is abolished or dampened. In case of continuing hemorrhage after administration of heparin, protamine injections must be repeated.

Discussion

With increasing experience we have developed certain guiding principles which of course may have to be modified in the light of further observations. In addition to the factors enumerated in table 1, weight is an important factor in determining heparin response. This is illustrated by patient Wm. P., who received preoperatively 400 mg. of Depo-heparin without vasoconstrictors, resulting in a capillary coagulation time of 32 minutes with a duration of effect to 38 hours, and a large hematoma at the site of injection. The amount he received was equivalent to 3.5 mg. per pound of body weight. in our opinion 2 mg. per pound is sufficient as a preoperative or therapeutic dose. Postoperatively, even the 2 mg. per pound weight dose may be too much, as shown by the case of Vesta W., who received 300 mg. of Depo-heparin (1.71 mg. per pound of body weight) and developed a huge hematoma in the incision of a lumbar sympathectomy. This patient had no thrombosis at the time, but had had this condition in the past. In postoperative prophylaxis 1 mg. of heparin per pound of body weight is a safer daily dose.

This matter raises the question of the advisability of giving large doses of heparin intramuscularly the absorption of which is not under any further control than that given by the gelatin-dextrose menstruum and the vasoconstrictor. However, even with 200 mg. given in 10 per cent aqueous solution, we have observed a severe hemorrhage from an unsuspected cervical erosion in Viola M., who required several transfusions to restore her blood count.

In addition, heparin seems to have a cumulative effect, because a patient whose coagulation time has returned to normal may respond the second and third time with a far longer coagulation time or even with hemorrhage. There are several possible explanations for this which we plan to investigate in the future. Suffice it to say here that, once the patient has received a large dose of heparin, the heparin requirement diminishes, and the return of the capillary coagulation time to a normal level does not mirror the increased sensitivity. Increased heparin sensitivity may be due to several factors, some of which are listed in table 1. From the standpoint of avoiding hemorrhages after heparin administration the following points need emphasis: (1) Small amounts

of heparin remain in the blood stream, although only a single dose of heparin is given for a longer time than venous or capillary coagulation times can detect them. They are demonstrable, however, with a heparin clotting time or heparin titration.* (2) After certain shocklike states, including coronary thrombosis, pulmonary embolism and massive peripheral thrombosis, anticoagulant substances appear in the blood,[10] and they may manifest themselves by increased reactivity to heparin (case 10 of figure 3, and cases 3 and 9 of figure 2). We have again and again seen astonishing responses to heparin after the 10 mg. test dose in patients who were recovering from or had just suffered an acute thrombosis. In such patients

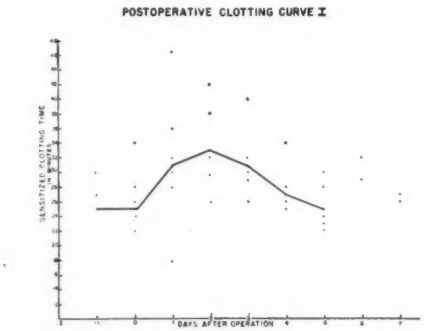

FIG. 10. Prolongation of sensitized clotting times following operations. Straight line represents average curve of 7 patients. This is a frequent response.

the prothrombin level may also drop as we have observed after coronary occlusion; the heparin-retarded clotting time lengthens following operations, suggesting the appearance of antithrombic substances (fig. 10).

The site of injection may show hematomata, which is very infrequent, but it is to be noted that, if any other hypodermic or other form of injection is given, large hematomata may occur even when coagulation times are not excessively prolonged. It is known that massive hemorrhages may be produced by paravertebral sympathetic blocks under dicumarol[11] and this seems to be true when too much heparin is administered.

* Unpublished Data.

This brings us to the important question: what is the desirable range of capillary coagulation time, a range which is both safe and protective against thrombosis or extension of thrombosis? Our experience, extending over 12 years, indicates that for therapeutic purposes a range between 8 and 12 minutes is effective. There is no need to reach peaks of 20 to 30 minutes. This is uneconomical because so much more of the drug will be excreted through the kidney. Therefore, the plateau type of curve is preferable. The heparin-gelatin emulsion is sometimes painful. While it is a definite improvement over the Pitkin menstruum, our records indicate a 15 per cent incidence of pain of which patients spontaneously complain, some of course more bitterly than others.

CONCLUSIONS

A study of the graphs presented indicates that the variability of the patient's response to heparin is great. The value of mass statistics, transferred to punch cards and analyzed for statistical significance, is not questioned; but they will not substitute for a close clinical observation of each patient receiving anticoagulants. The balance of coagulant and anticoagulant factors is delicate and seems to swing spontaneously; the administration of an anticoagulant markedly influences this balance.

Regarding dosage schedules, the following tentative schedule has been followed: a priming dose of intravenous heparin (30 to 50 mg.) is followed by the deep subcutaneous injection of heparin in gelatin. The initial priming dose will raise the capillary coagulation time to 8 to 12 minutes and this should be maintained with the average daily dose of 2 mg., with vasoconstrictors, per pound of body weight. This dose refers to the treatment of acute thrombotic episodes and must be kept up for 14 days. Shorter periods of administration will give rise to the recurrence or flare-up of the thrombosis, when heparin is discontinued. This statement refers to surgical patients; after coronary thrombosis, four weeks seems to be a safer period.

One mg. per pound of body weight is a good average prophylactic daily dose. In the presence

of an open lesion, or of a recent surgical incision, this dose must never be exceeded, but may even be split by giving it every second day.

Control of the clotting mechanism is sufficiently safe if a capillary coagulation time is determined once a day, usually in the morning, with the heparin administered at noon-time. When a sensitized clotting time is used, this too can be run once a day and should be kept at the upper limit of normal. Such a control leads to smaller prophylactic doses than have been employed in the past.[9]

Aside from occasional sensitization to heparin, the only complication of heparin administration is hemorrhage. The following precautions are useful in minimizing this untoward reaction: (1) heparin should be administered according to body weight; (2) following trauma, operation or acute vascular accidents, natural anticoagulants may potentiate the effect of heparin; (3) protamine sulfate should always be on hand and its injection repeated every four hours until hemorrhage stops; (4) hemorrhage continuing in spite of administration of protamine is a rare self-perpetuating mechanism uninfluenced by neutralization of heparin which must be combated by blood transfusions.

Summary

An emulsion of heparin in gelatin, given with a daily control of capillary coagulation times, is a simple efficient anticoagulant therapy. The great variability of response to heparin makes set schedules of dosage impossible. The therapeutic dose should always be double the prophylactic dose; in the case of an acute thromboembolic episode, the administration of heparin should be maintained for two weeks. The determination of heparin tolerance gives a good insight into the state of the clotting mechanism; it can be done in vivo or in vitro.

Acknowledgment

The technical assistance of Mrs. Jeannette Pearson Leavens is hereby gratefully acknowledged.

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Oxygen Tension of Tissues by the Polarographic Method

II. Detection of Right to Left Shunts by Changes in Skin Oxygen Tension Resulting from Inhalation of Oxygen

By HUGH MONTGOMERY, M.D., HARRY F. ZINSSER, JR., M.D., AND ORVILLE HORWITZ, M.D.

Normal individuals breathing pure oxygen obtain full saturation of their hemoglobin, whereas those with right to left shunts do not. Oxygen hemoglobin dissociation curves indicate that increases to full oxygen saturation of hemoglobin are accompanied by marked increases of the oxygen tension. When breathing oxygen fails to produce full saturation, relatively little change in oxygen tension occurs. When the cutaneous circulation is rapid, changes in skin oxygen tension have been shown to vary directly with changes in blood oxygen tension. Taking advantage of these facts the authors have described a method of detecting significant right to left shunts by polarographic measurements of skin oxygen tension.

IT HAS long been known that right to left shunts lower the arterial oxygen saturation. The essential factors involved in this phenomenon were presented in the Lundsgaard and Van Slyke monograph of 1923.[1] More recently, certain technics such as the exercise test[2, 3] and the test utilizing inhalation of 100 per cent oxygen[4–6] have been employed in the detection of right to left shunts. In the presence of such shunts, these tests demonstrate changes in the arterial oxygen saturation that are considered diagnostic. The changes in arterial oxygen saturation have been measured either by chemical analysis of arterial blood samples or by use of the oximeter.[6–8] When the oximeter is used, the necessity for repeated arterial sampling is eliminated, although an initial arterial sample must be analysed to permit standardization of the instrument.

The oxygen inhalation test for the recognition of right to left shunts is based on the failure of patients with such shunts to achieve full arterial oxygen saturation in contrast to nonshunt patients who develop 100 per cent saturation.[4, 5] The nature of the oxygen dissociation curve[9, 10] is such that the increase to 100 per cent oxygen saturation occurring in nonshunt patients, when they inhale oxygen, often involves only a small change in oxygen saturation. For the same degree of change on the curve, oxygen tension measurements would show greater differences. The polarographic method permits estimation of changes in arterial oxygen tension by measurements of oxygen tension in skin having a fast circulation.[11] Therefore, studies were conducted using the polarographic technic to measure the effect of oxygen inhalation on the skin oxygen tension of patients with and without right to left shunts.

METHODS

The polarographic method for measuring oxygen tension of skin has been described in detail.[11] In the present study, however, no attempt is made to convert readings to absolute values of oxygen tension in millimeters of mercury. Rather, the results during inhalation of oxygen are expressed simply in terms of percentage increase over the control galvanometric readings obtained during breathing of room air. Measurements were made in duplicate using two electrodes in order to minimize the chance for error resulting occasionally from inactivation of an electrode by extravasated blood at its tip.[11] In each instance, the results recorded from the less actively responding electrode were discarded.

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Estimations of cutaneous circulation were made by pyrometric measurements of environmental and skin temperature.[12] In all experiments, the patient was kept warm to assure the fast skin circulation which is necessary to make skin oxygen tension approximate that of arterial blood.[11] In all but one patient the skin temperature of the forearm exceeded the environmental temperature by at least 4 degrees Centigrade.

Oxygen for inhalation was administered as 100 per cent oxygen utilizing a demand valve mask when a good facial fit of the mask was obtainable. Otherwise, oxygen was administered through an oronasal B-L-B mask at 15 liters per minute with considerable wastage.

In most of the patients, analyses of arterial oxygen saturation were made before and during inhalation of 100 per cent oxygen, to provide further control of the study. These values were derived from measurements of oxygen content and capacity of blood specimens obtained anaerobically from the brachial or femoral artery.[13] Specimens were analyzed promptly or were kept in ice water for short periods of time before analysis. In most instances a modification of the manometric method of Van Slyke and Neill was used.[13] In a few experiments the spectrophotometric method was employed.[14]

TABLE 1.—*Patients with Right to Left Shunts*

Patient, Age and Sex	Diagnosis	Presence of right to left shunt proved by:	Hemoglobin in Grams	% Arterial O_2 Saturation Breathing		Temp. Skin °C.	Temp. Room °C.	Per Cent Rise Skin Oxygen Tension
				Air	100% O_2			
A. M., 33, Male	Eisenmenger Complex	Angiocardiography Card. Catheterization Circulation times Exercise Test	23.9	78.4	87.5	31.5	26	25
J. G., 17, Male	Tetralogy of Fallot	Angiocardiography Circulation times	26	82	86.5	32	26	20
M. S., 9, Male	Multiple defects. Probable Tetralogy of Fallot plus double aortic arch and patent ductus arteriosus.	Angiocardiography Card. Catheterization Circulation times	15.5	87	—	31	23.3	16
L. A., 17, Female	Tetralogy of Fallot	Angiocardiography Circulation times	22.3	89	—	28.5	23.5	42
R. T., 5, Male	Tetralogy of Fallot	Angiocardiography Circulation times	17.7	69	—	31	26	33
D. B., 16, Male	Eisenmenger Complex	Angiocardiography Card. Catheterization Circulation times	18.6	77.8	84	31	23	26
A. B., 7, Female	Tetralogy of Fallot	Angiocardiography Circulation times	16.8	88	—	30	25	25

Investigative Procedure

The patient was permitted to sit, recline, or lie supine according to his comfort. The loose skin of the forearm was then punctured to approximately two-thirds its thickness by a 25 gage needle to facilitate insertion of an electrode through the resulting hole. The fingertips were submerged in the saline bath that completes the circuit. Galvanometric readings were taken until a satisfactory control level was established. The patient then inhaled oxygen for 15 minutes, after which he resumed the breathing of room air. Readings were taken at approximately two minute intervals before, during, and after oxygen inhalation, and continued until such time as they returned to constant values near the control level.

Subjects

Seven patients who had congenital cardiac disease with right to left shunts were studied. Proof of such a shunt was established beyond

question in every patient by angiocardiographic demonstration of an overriding aorta,[15] and by the finding of circulation times characteristic of such shunts.[16] In 3 of the patients, additional confirmation was provided during cardiac catheterization: in one when the catheter was passed into the overriding aorta, and in 2 by the finding of identical right ventricular and systemic arterial systolic pressures, indicating dextroposition of the aorta.[17] (See table 1).

TABLE 2.—*Patients without Right to Left Shunts*

Patient, Age & Sex	Diagnosis	Hemoglobin in Gm.	% Arterial O_2 Sat. Breathing		Temp. Skin °C.	Temp. Room °C.	Per Cent Rise Skin O_2 Tension
			Air	100% O_2*			
R. H., 8, Male	Isolated Pulmonary Stenosis	11.7	97.8	100 (1.46)	30	25	337
E. S., 22, Female	Atrioseptal Defect	12.8	90.0	—	30.5	25.5	210
J. B., 28, Male	Mitral Stenosis with congestive failure	15.2	95.2	100 (1.50)	31.5	24	180
D. H., 46, Female	Mitral Stenosis	12.8	96.6	100 (2.08)	33	24	460
N. W., 32, Male	Mitral Stenosis with congestive failure	14.9	99.5	100 (1.91)	29.5	26	100
C. G., 31, Female	Mitral Stenosis with congestive failure	16.8	—	—	30	26	712
M. H., 34, Female	Mitral Stenosis and Polycythemia	18.7	95.4	100 (1.98)	32.5	27.5	206
R. R., 16, Female	Mitral Stenosis with congestive failure	12.6	96.6	100	30.5	25.5	136
R. Q., 39, Male	Mitral Stenosis with congestive failure	16.1	—	—	32	24	230
F. P., 55, Male	Coronary occlusion with cyanosis	12.0	—	—	31.5	26	500
V. C., 45, Female	Sarcoidosis with pulmonary fibrosis	16.0	—	—	30.5	25	250
J. M., 26, Male	Tuberculosis with pulmonary fibrosis and polycythemia	19.3	91.8	100 (2.3)	33.5	26	460
A. T., 66, Male	Silicosis and Pulmonary Emphysema	14.4	94.6	100 (1.6)	34	26	130
L. D., 57, Male	Pulmonary Emphysema	14.2	95.4	100 (2.05)	34	22	150
G. R., 52, Male	Post-pneumonectomy	10.7	90.0	100 (1.72)	34.5	26	450
M. S., 64, Female	Diabetes Arteriosclerosis Cellulitis of toe	13.1	97.9	100 (1.8)	32	25	480
M. C., 52, Female	Post-menopausal bleeding	12.1	95.2	100 (1.8)	29.5	24.5	152
S. K., 68, Female	Cystocele	12.6	94.9	100 (1.9)	32	27	366
C. W., 61, Male	Ganglion right foot	13.6	98.0	100 (1.8)	31	25	823
C. S., 51, Male	Thromboangiitis obliterans with gangrene of foot	13.7	—	—	29	21.5	250

* The figures in parentheses represent the excess oxygen in volumes per cent after saturation of hemoglobin had been accomplished.

Twenty control subjects not having right to left shunts were chosen from patients in one of

three categories: (a) 5 in whom no cardiac or pulmonary disease was found, (b) 10 with cardiac disease, and (c) 5 with disease primarily involving the lungs.

No systematic study of entirely normal subjects is included here because it was previously shown that oxygen inhalation produced striking elevations of oxygen tension as measured polarographically in the warm skin of normal individuals.[11]

Results

Measurements of skin oxygen tension during oxygen inhalation showed a sharp difference in response between the controls and the group of patients with right to left shunts. No patient with such a shunt was able to double the preinhalation level of skin oxygen tension at any time during inhalation of oxygen. The greatest rise in this group was a 42 per cent increase with an average rise of 29 per cent. Every patient in the control group, on the other hand, developed levels of skin oxygen tension at least double those of the preinhalation period. The smallest rise in this group was 100 per cent, and the average rise was 314 per cent. The difference between the two groups is so obvious that statistical analysis would be superfluous.

When arterial oxygen saturation was measured before and after oxygen inhalation, all those with right to left shunts failed to become fully saturated, while all those of the control group increased to 100 per cent saturation.

These results are shown in detail in tables 1 and 2.

Discussion

The skin oxygen tension of patients with right to left shunts does not increase in a normal fashion during the inhalation of 100 per cent oxygen. The abnormality in response is so marked as to provide another test for use in the recognition of patients with right to left shunts. This test furnishes certain distinct advantages over other methods employed to detect such shunts: in addition to being objective, it is safer, quicker, requires less cooperation by the patient, eliminates arterial or venous punctures, and causes considerably less discomfort. These advantages are particularly desirable since so many of the patients are children requiring study at an age when other procedures are difficult, at best. The children who have been subjected to this test did not seem to be appreciably disturbed and were content to remain still throughout the procedure.

While all right to left shunts in the present study were intracardiac, extracardiac shunts of right to left type would be expected to give similar results. Thus, the method would in no way differentiate between the right to left shunts of congenital cardiac disease and other conditions permitting significant amounts of unaerated blood to reach the peripheral circulation.

Certain technical errors can result in measurements simulating the type of response seen in the presence of right to left shunts. Chief among these is inactivation of an electrode by improper insertion or by a drop of blood at its tip. Throughout the study two electrodes were used simultaneously to reduce the chance for such an error. In later work, more electrodes are being used, and this is to be recommended, particularly when the procedure is carried out by a technician. In place of increasing the number of electrodes, the measurements may be repeated using a different site in either arm. The other potential source of error lies in the improper administration of oxygen by a poorly fitting demand valve mask.

In the present study, all the right to left shunts were known to be of significant degree. Smaller shunts might not be detectable.

Summary

1. Polarographic measurements of skin oxygen tension were made during the inhalation of 100 per cent oxygen on patients with proved right to left shunts.

2. The increase in skin oxygen tension of such patients averaged 29 per cent above the preinhalation measurements.

3. This response differed sharply from the significantly greater rise seen in 20 patients without right to left shunts.

4. The method therefore permits detection of right to left shunts of significant degree and

presents certain distinct advantages over other methods.

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The Effect of Smoking upon Blood Flow in the Sympathectomized Limb

By SAMUEL I. RAPAPORT, M.D., HUGH A. FRANK, M.D., AND THEODORE B. MASSELL, M.D.

The effect of smoking upon the blood flow of a sympathectomized limb was examined in 19 patients. Sympathectomy was found to abolish the peripheral vasoconstriction produced by smoking. The constriction, therefore, is mediated by sympathetic vasomotor fibers and not by humoral agents such as adrenaline or posterior pituitary hormone. There is no difference in the response of patients sympathectomized for thromboangiitis obliterans, arteriosclerosis or severe vasospasm. The relation between the vasoconstrictor effect of smoking and the action of tobacco in thromboangiitis obliterans is discussed.

THE PERIPHERAL vasoconstriction produced by smoking has been known for many years. Most investigators[1–5] have found this constriction due to the action of the absorbed nicotine; and not, as some have claimed, [6,7] the result of sympathetic reflexes initated by the breathing pattern of smoking or by the irritation of the smoke itself. Goetz[8] reported that the constriction at the very onset of smoking is of such reflex origin, while the more marked decrease in blood flow which follows is due to the sympathomimetic action of the absorbed nicotine.

Nicotine in the amount inhaled from one or two cigarettes acts as a general synaptic stimulant. As such, in theory, it could produce peripheral vasoconstriction by four known mechanisms: (1) by the excitation of central vasomotor centers, (2) by a direct stimulation of sympathetic ganglia, (3) by an increased production of adrenaline, and (4) by the liberation of posterior pituitary hormone. The first two of these mechanisms require an intact sympathetic nerve supply to the blood vessels. The third and fourth are humoral and should not be abolished by sympathectomy. Rather, sympathectomy has been said to increase the sensitivity of blood vessels to the vasoconstrictor effects of adrenaline,[9,10] although this is questionable.[11] About 50 milliunits of posterior pituitary hormone are said to be liberated by the smoking of one or two cigarettes.[12] This is the equivalent in man of the amount found to decrease coronary blood flow in the dog. It seemed possible that it should also produce peripheral vasoconstriction.

The present experiments were conducted to answer the question—does the vasoconstrictor response to smoking persist after sympathectomy, i.e., is its mechanism nervous or humoral? This question has clinical as well as theoretic interest. While it is generally recognized that tobacco accelerates the disease process of thromboangiitis obliterans, the manner in which it does so is unknown. There are observations to suggest that it is unrelated to vasoconstriction. In the first place, while there is a marked individual variation in the degree of vasoconstriction produced by smoking, there is no clear cut distinction between normal smokers and patients with thromboangiitis obliterans.[3,13–15] Secondly, Abramson and his coworkers[16] have shown that the vasoconstriction of smoking is limited to the skin. Blood flow through muscle is not reduced. Yet muscle vessels are also involved in the thromboangiitic process.

There are recent reports in which the failure of sympathectomy to afford relief in a small percentage of patients with thromboangiitis obliterans has been attributed to continued smoking. Freeman[17] described good results from

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sympathectomy in 16 patients who stopped smoking but not in 3 who continued to smoke. In a recent panel on peripheral vascular disease[18] there was general agreement that smoking after sympathectomy resulted in a progression of the disease. If tobacco can continue to exert its pernicious effect in this disease in the sympathectomized limb, it seemed important to determine whether or not vasoconstriction could also be demonstrated in such a limb.

The data in the literature on the response to smoking after sympathectomy are scanty and conflict. Maddock and Coller[1] could not demonstrate vasoconstriction on the operated side in a patient with a cervicodorsal and lumbar sympathectomy for Raynaud's disease. They also observed in 2 patients that sympathetic nerve block with procaine eliminated the constriction. However, the sensitivity of blood vessels after the removal of sympathetic control changes with time,[19] and it is not safe to assume that a response observed acutely following a sympathetic block will persist after sympathectomy. Theis and Freeland[20] reported the opposite—a patient with an upper thoracic sympathectomy for Raynaud's disease in whom smoking produced a sharp decrease in skin temperature. They offered no evidence to exclude the possibility of regeneration, a point of particular concern in upper thoracic sympathectomy.[21] Goetz[8] stated that vasoconstriction was delayed but not abolished after sympathectomy.

We have observed the effect of smoking upon skin temperature and blood flow in 18 patients after lumbar sympathectomy and one patient after an upper thoracic sympathectomy. Six of these had arteriosclerosis obliterans, 6 had thromboangiitis obliterans, while 7 were operated on for severe vasospasm. They were so chosen to evaluate any differences due to the underlying disease process. The elapsed time between surgery and the experiment varied from 4 days to 26 months. In some patients L-3 was the lowermost ganglion removed, while in others L-4 was also excised. In the latter the postganglionic fibers to the second toe, the toe whose blood flow was measured, may have been interrupted.[22]

Experimental Procedure

The test was performed in the early afternoon. The patient went without lunch and did not smoke for several hours. No medication was given during that day, and no sedation the night before. All of the subjects had been habitual smokers, although several had stopped some months earlier. An attempt was made to start the experiment with the room temperature about 80 F. Usually it was impossible to prevent a variation of room temperature of one or two degrees during the test. However, this was not felt to be a source of error, since the sympathectomized limb is not subject to changes in blood flow produced by thermal reflexes.

The patient, clad in light pajamas, rested quietly in the supine position. Thermocouples were attached to the big toe of each foot and to a forefinger. A fourth thermocouple measured room temperature. Temperatures were recorded in rotation, one each minute, upon a Leeds and Northrup self-balancing potentiometer (Micromax). Pulse volume and blood flow measurements were taken from the second toe of the sympathectomized foot by the use of a Burch-Winsor pneumoplethysmograph.[23] A 5 cc. volume of toe was measured by displacement of an aqueous solution of gentian violet. The plethysmograph cup was then fitted to the stained portion of the toe and an air-tight seal between the cup and toe was made with a nonhardening calking compound (Kalkkord).

Blood flow was measured by the venous occlusion method as described by Goetz.[24] The occlusion cuff was placed at the ankle and a pressure of 45 mm. Hg was applied suddenly from a reservoir. Since, in our experience, the "straight line" portion of the rise after venous occlusion is often very short, a line drawn tangent to that portion of the curve, at least 2 pulse beats in length, which showed the maximum rise was taken as the best approximation of blood flow. The values so obtained were multiplied by 3 to correct for the placement of the cuff at the ankle, instead of the base of the toe[24]; and are expressed in cc. per minute per 100 cc. of part.

At the beginning of each experiment the completeness of sympathectomy was checked by the immersion of one hand in ice water for one minute. This results in a sudden reflex fall in pulse and part volume in the intact digit, but not in a sympathectomized digit. In every instance the temperature of the sympathectomized extremity was considerably above that of the opposite extremity and above room temperature.

The patient rested at least 30 minutes after the cold immersion test before beginning to smoke. During this period from two to eight blood flow determinations were made. In most, three blood flow measurements were made at one to two minute intervals 15 and 30 minutes after the cold immersion. Blood pressure and pulse rate were recorded.

The patient was then allowed to smoke two cigarettes in succession. He was instructed to inhale but otherwise was permitted to smoke in his own manner. The pulse volume was recorded continuously except when venous occlusion measurements were being made. In some experiments these were taken after each cigarette and 15 to 20 minutes after smoking. In others, venous occlusion measurements were taken every two minutes during the period of smoking and again 15 to 20 minutes later. Blood pressure was noted just before or just after each venous occlusion.

Results and Discussion

Without exception the skin temperature of the sympathectomized limb did not fall during or after smoking. This is illustrated in figure 1, which is a graph of the temperature response of a sympathectomized toe and of an intact

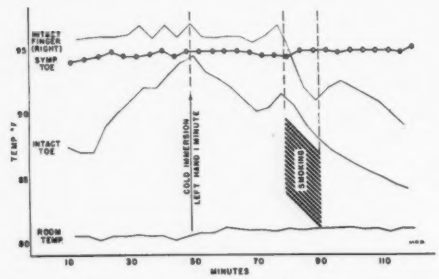

Fig. 1. Effect of smoking on skin temperature. Subject J. Y.

finger and toe. The room temperature was 81 F. and the sympathectomized toe stayed between 94.5 and 95 F. Its temperature was not altered by immersion of one hand in ice water or by smoking. The finger tip, the vessels of which were fully dilated, did not change in temperature when the opposite hand was immersed in ice water. However, when smoking was started there was a sharp drop in finger tip temperature. The temperature of the intact toe was rising when the hand was immersed. A prompt fall resulted which continued for about 20 minutes. The fact that cold immersion produced a fall in toe but not in finger temperature is an illustration of the general rule that the effect of any stimulus upon arteriolar tone is modified by the preexisting state of the vessels. Vessels which are between constriction and full dilatation often show a marked response to vasoconstrictor stimuli which will evoke only a transitory response from fully dilated vessels. When the intact toe temperature began to rise again the subject was permitted to smoke. There was a second sharp fall in skin temperature which persisted until the experiment was stopped.

The skin temperature records of the other patients were similar to this example in so far as the sympathectomized limb is concerned. As expected, arteriolar constriction in the intact extremity during smoking was manifested by a drop in skin temperature of from 1.5 to 11 F. In a few instances the skin temperature of the intact extremity prior to smoking approached that of the room. In the presence of this degree of vasoconstriction no further constriction during the period of smoking could be demonstrated by the skin temperature method.

The plethysmographic tracings demonstrate that blood flow in the sympathectomized digit is not diminished by smoking. Figures 2 and 3 show the type of pulse volume and venous occlusion tracings which were obtained; and the failure of smoking to decrease the venous occlusion slope. These tracings also illustrate the fact that the pulse volume deflection is not necessarily a measure of the rate of blood flow.[25] In figure 2 there is a large pulse deflection while in figure 3 it is practically indistinguishable. Yet the blood flow rates in the 2 patients are within the same range. The pulse volume deflection is a measure of the difference between arterial inflow and venous outflow throughout the pulse cycle. In the first patient the large vessels are patent, and with each heart beat most of the blood enters the toe rapidly over a short period of time. The large vessels of the second patient are sufficiently occluded by arteriosclerotic plaques to prevent a rush of blood into the toe with systole. Although a large amount of blood is provided the toe through the small collateral vessels opened by sympathectomy, the flow through these vessels is slower and more evenly distributed throughout the pulse cycle. At no time during the cycle is there a large difference between the rate of arterial inflow and venous outflow; hence, the pulse volume deflection is small.

Moreover, figure 2 illustrates a common find-

ing: a decrease in pulse volume without a corresponding reduction in blood flow. (Compare control tracing with that after the second cigarette.) The reason for this is not completely understood. It appears to depend in part upon a corresponding increase in heart rate which damps fluctuation by decreasing both the stroke volume and the venous emptying between beats. It would seem that when there is a change in heart rate, such as the increase of 5 to 20 beats per minute which occurs during smoking, change in the height of the pulse volume must be interpreted with care.

The individual blood flow measurements and their averages are listed in table 1. In this table the abbreviations AO, TAO, and Vspm refer to arteriosclerosis obliterans, thromboangiitis obliterans and vasospasm, respectively. The time between sympathectomy and the experiment is listed to the nearest day, week or month. Under the heading level of sympathectomy the upper and lowermost ganglia removed are tabulated. These levels were confirmed by roentgen visualization of dura clips placed at operation. Room temperature is abbreviated as R.T. Blood flow is in cc. per minute per 100 cc. of tissue. Control blood flows are at 15 and 30 minutes after the cold immersion test. Under the headings 1st and 2nd are listed the blood flow measurements taken either during or immediately after each cigarette. The averages are given in separate columns.

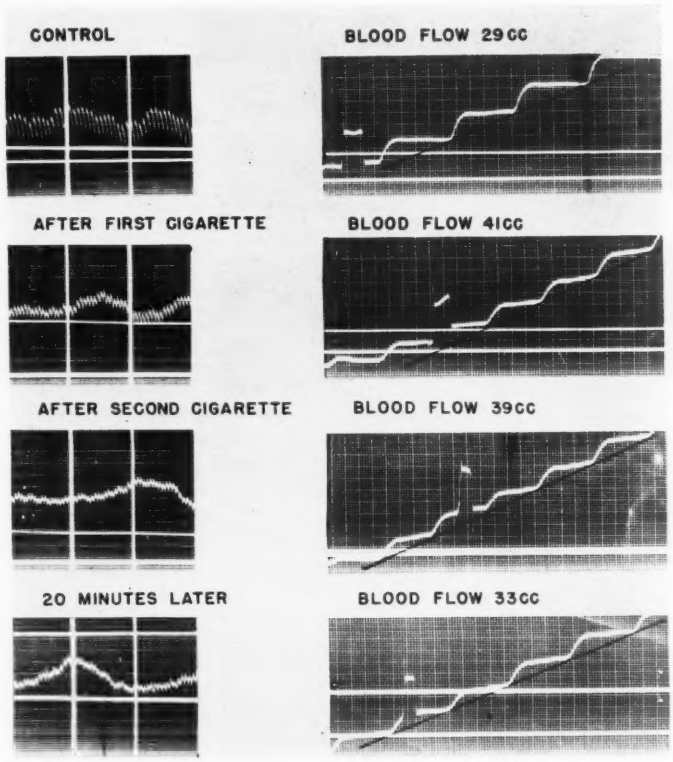

FIG. 2. Subject J. W. Pulse volume tracings are shown in the left hand column; venous occlusion tracings on the right. For details see text.

These data show that smoking did not decrease blood flow in 18 of 20 experiments. The 2 exceptions, V. W. and A. H., appeared clinically to have been completely sympathectomized, but in each, vasomotor reflexes were demonstrated. For example, patient V. W. had a

toe temperature on the operated side of 92 F., while on the unoperated side the temperature of the toe was that of the room, 77 F. Yet, as shown in figure 4, immersion of one hand in ice water produced a transient reflex vasoconstriction in the supposedly sympathectomized toe. This indicated that some sympathetic fibers were still intact; the fall in blood flow which occurred during smoking could have been the result of their stimulation. Such a case

remaining 18 experiments are summarized in figure 5. In this graph the blood flow 15 minutes after cold immersion has been given a value of 100 per cent. Subsequent readings are expressed in per cent of this. The scatter graph shows the distribution of blood flow for the individual patients, the bar graph the averages for the group. Since the error in blood flow measurement in our hands was approximately 20 per cent, the small apparent increase in blood flow

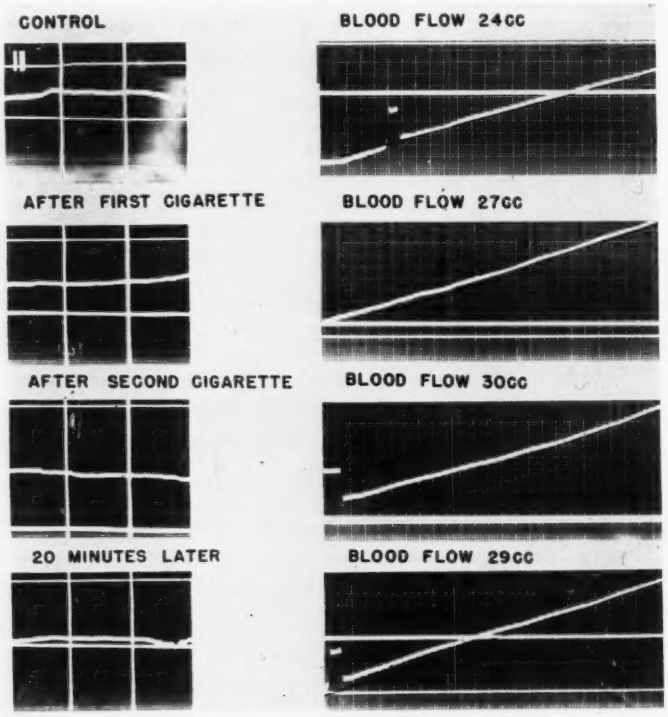

FIG. 3. Subject S. E. Pulse volume tracings are shown in the left hand column; venous occlusion tracings on the right. For details see text.

points out the necessity of establishing the completeness of sympathectomy by an attempt to elicit vasomotor reflexes. It is also of interest in that a diminution in blood flow of over 40 per cent during the period of smoking was not accompanied by a drop in skin temperature. This illustrates the insensitivity of skin temperature as an index of blood flow in the room temperature range, a point emphasized by Fetcher.[26]

The average blood flow measurements of the

during and after smoking is not statistically significant. Yet it is conceivable that flow does actually increase in the sympathectomized vascular bed as the result of vasoconstriction in unsympathectomized areas, and of the small rise in blood pressure which occurs (average systolic increase 9 mm., average diastolic 4 mm. Hg). In any event, the apparent increase makes it unlikely that any real decrease could have been masked by experimental error.

These observations demonstrate that the

TABLE 1

Subj.	Diag.	Time	Level of Symp.	R.T.	Blood Flow cc./min./100 cc.									
					Individual					Average				
					Control		Smoking		After	Control		Smoking		After
					15m	30m	1st	2nd	15–20m	15m	30m	1st	2nd	15–20m
J. P.	AO	4d	L2–L3	79–82	36	39	39	54	51	37	42	42	52	51
					38	44	44	51	47					
					—	—	—	50	57					
					—	—	—	—	47					
					—	—	—	—	47					
					—	—	—	—	54					
J. P.	AO	10d	L2–L3	83	65	—	66	63	65	67	—	68	68	65
					69	—	63	68	62					
					—	—	75	74	69					
	AO	20d	L1–L3	83–85	14	—	14	19	20	17	—	16	20	22
					18	—	19	21	24					
					20	—	16	21	23					
H. B.	AO	7w	L1–L4	82	10	12	12	10	11	10	12	12	11	11
					9	11	11	11	12					
					10	12	12	11	11					
					10	11	12	11	11					
F. M.	AO	9w	L1–L3	80–82	14	20	21	24	23	15	20	23	23	22
					15	20	26	21	21					
					17	20	21	23	21					
W. F.	AO	10w	L1–L3	83–85	5	8	8	8	9	6	8	8	8	9
					8	7	7	10	10					
					5	8	8	8	7					
					5	8	—	8	10					
S. E.	AO	9m	L2–L4	83	24	24	27	30	27	26	24	27	31	28
					26	24	27	30	30					
					27	24	27	30	25					
					—	26	27	33	29					
					—	—	—	—	29					
C. G.	TAO	7w	L3–L4	82	15	—	23	26	24	20	—	20	22	22
					21	—	17	17	21					
					22	—	20	22	22					
					20	—	—	—	20					
L. P.	TAO	7w	L3–L4	81	62	70	84	92	78	64	72	83	88	78
					65	71	79	83	80					
					65	77	86	87	81					
					—	—	—	90	75					
H. M.	TAO	20w	L1–L3	74	37	43	45	52	46	37	43	46	47	44
					37	43	51	43	41					
					33	43	46	49	44					
					41	—	45	46	43					
J. W.	TAO	11m	L2–L3	82–84	27	29	45	36	36	26	30	41	38	37
					26	27	41	39	39					
					—	29	35	37	39					
					—	35	39	44	33					
A. S.	TAO	12m	L2–L4	81	45	41	50	41	50	43	44	48	44	51
					44	47	45	47	51					
					41	45	—	—	—					
H. R.	TAO	26m	Upper Thor.	80–82	37	37	37	33	36	31	37	35	37	32
					30	38	33	36	32					
					29	37	36	38	30					
					26	37	33	42	30					

TABLE 1.—*Continued*

Subj.	Diag.	Time	Level of Symp.	R.T.	Blood Flow cc./min./100 cc.									
					Individual					Average				
					Control		Smoking		After	Control		Smoking		After
					15m	30m	1st	2nd	15–20m	15m	30m	1st	2nd	15–20m
V. W.	Vspm	11d	L2–L4	77–81	—	38	29	21	25	—	38	27	22	26
					—	38	32	17	24					
					—	35	23	25	28					
					—	—	23	26	29					
W. S.	Vspm	2w	L2–L3	78–80	17	22	23	34	24	20	24	30	32	26
					25	20	36	29	29					
					18	30	—	—	26					
R. R.	Vspm	13w	L2–L3	82–84	29	35	36	47	36	31	35	41	47	37
					32	40	46	47	38					
					32	32	—	—	—					
M. B.	Vspm	10m	L2–L4	82–84	54	47	53	53	63	56	49	53	55	58
					63	51	60	45	61					
					51	50	53	63	51					
W. W.	Vspm	11m	L2–L3	80–83	44	38	41	41	48	41	37	42	40	55
					38	38	42	39	60					
					—	35	—	—	—					
J. Y.	Vspm (poss TAO)	17m	—	80	11	—	6	8	7	8	—	7	8	8
					8	—	8	9	9					
					7	—	8	8	8					
A. H.	Vspm	20m	—	80	32	32	21	29	25	30	30	23	28	26
					30	28	25	26	27					
					28	31	—	—	27					

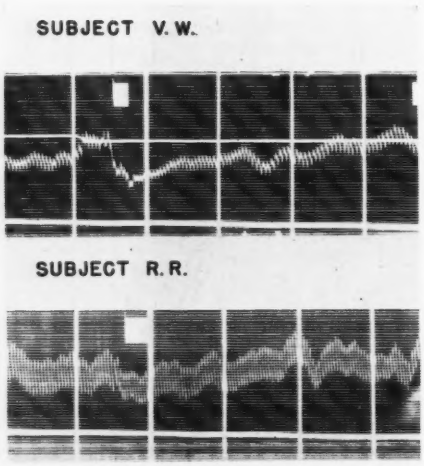

FIG. 4. Effect of immersion of one hand in ice water (first white marker) on the pulse volume tracing of a toe in two patients. The upper tracing shows the response in an incompletely sympathectomized extremity. The lower tracing shows the lack of response when sympathectomy is complete.

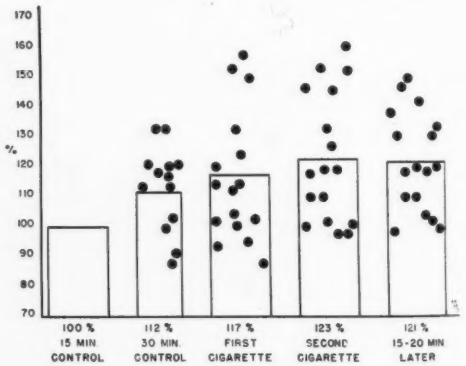

FIG. 5. Average blood flow as per cent of average initial control blood flow.

vasoconstrictor effect of smoking requires an intact sympathetic nerve supply to the blood vessels. It is not due to humoral mechanisms such as increased adrenaline production or liberation of posterior pituitary hormone. There is no difference in the response of patients sympathectomized for thromboangiitis obliterans, arteriosclerosis obliterans, or severe vasospasm. Neither the time elapsed since surgery, nor the type of surgery, i.e., whether or not L-4 ganglion is removed, appears to affect the result.

The fact that the 6 patients with thromboangiitis obliterans exhibited the same lack of vasoconstriction as did the others, does not invalidate the clinical reports that smoking continues to be harmful in this disease in the sympathectomized limb. Nor should it be made the basis for permitting patients to smoke after sympathectomy. Rather, it is additional evidence that the harmful effect of smoking in thromboangiitis obliterans is not the result of the vasoconstrictor action of nicotine.

Summary

The effect of smoking upon the skin temperature and blood flow of a sympathectomized limb was examined in 19 patients. Sympathectomy was found to abolish the peripheral vasoconstriction produced by smoking. This constriction, therefore, is mediated by sympathetic vasomotor fibers and not by humoral agents such as adrenaline or posterior pituitary hormone. There is no difference in the response of patients sympathectomized for thromboangiitis obliterans, arteriosclerosis or severe vasospasm. These results are of clinical interest because of recent reports in which continued smoking has been suggested as the reason for the failure of sympathectomy to afford relief in some patients with thromboangiitis obliterans. For, if tobacco can aggravate the thromboangiitic process in a sympathectomized limb, the implication exists that the mechanism of its pernicious effect in this disease is independent of its known vasoconstrictor action in the intact limb.

Acknowledgments

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Myocarditis in Acute Infectious Diseases

A Clinical and Electrocardiographic Study

By Irving Fine, M.D., Henry Brainerd, M.D., and Maurice Sokolow, M.D.

Serial clinical and electrocardiographic studies were carried out on 84 patients suffering from a variety of acute infectious diseases. About one-third were found to have myocarditis on the basis of abnormal electrocardiograms. Abnormal physical findings were usually present. Evidence of congestive heart failure was uncommon. A group of patients subjected to artificial fever therapy did not manifest similar abnormalities.

MYOCARDITIS associated with acute infectious disease has been described frequently in the literature. Most of the reports, however, are incomplete, either because of lack of essential data (such as the age of the patient, existence of previous heart disease, serial clinical and electrocardiographic studies) or because of the variability of criteria used (both clinical and pathologic). None of these papers has described the use of unipolar leads in detecting myocarditis.

This study was undertaken with several purposes in mind: (1) to determine the frequency of myocarditis in a variety of infectious diseases as demonstrated by significant electrocardiographic abnormality; (2) to investigate the extent and nature of these electrocardiographic changes; (3) to attempt a correlation of clinical and electrocardiographic findings; (4) to attempt an estimate of the functional disturbance of the cardiovascular system produced by infectious disease.

The Frequency of Myocarditis in Infectious Disease

Burnett and Piltz[1] took serial electrocardiograms on 55 adults and 45 children, all of whom were having, or had recently had, an acute infectious disease—influenza, pneumonia, tonsillitis, otitis media and mastoiditis, poliomyelitis, or tuberculous peritonitis. Significant electrocardiographic abnormalities, consisting essentially of partial A-V heart block and inverted T waves, were shown by 20 of the adults and 8 of the children.

Masters and Jaffe[2] took daily electrocardiograms on patients with acute infectious diseases and found abnormalities in a large number. The authors gave no information as to the nature of the T-wave and RS-T abnormalities noted, nor whether the deviations reverted to normal.

Saphir[3] collected data on 5626 autopsies on patients who had died from a wide variety of unrelated diseases, including infections such as bacterial meningitis, pneumonia, and tuberculosis. He found that myocarditis occurred in approximately 4 per cent of the cases. Saphir, Wile, and Reingold,[4] in a study of 1420 routine autopsies on children who had died of poliomyelitis, diphtheria, pneumonia, meningitis, pyemia, tuberculosis, bacterial endocarditis, or rheumatic fever found myocarditis in 6 per cent. The authors stated that the most significant single sign of myocarditis is a tachycardia out of proportion to temperature, since this phenomenon was present in one-half the patients in their series. Symptoms of cardiac failure were almost exclusively confined to patients with rheumatic heart disease or bacterial endocarditis. They concluded that myocarditis produces no characteristic symptoms, but that its presence should be suspected in any patient suffering from an acute infectious disease who, suddenly and without apparent reason, becomes worse.

In a recent study, Saphir[4] described the characteristic heart in myocarditis as enlarged, with a soft, greyish yellow myocardium and a few yellowish streaks or minute areas of hemorrhage. Because often the disease process can

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be detected only by histologic examination, he emphasized the need for careful scrutiny of a number of tissue slides. Gore and Saphir[4] reported that of 1402 instances of myocarditis collected at the Army Institute of Pathology over 90 per cent were nonrheumatic.

Neubauer[5] stated that acute infectious disease is the most important cause of myocarditis. He stressed the belief that the electrocardiogram can demonstrate this condition when clinical signs are slight, doubtful, or absent. In his study of 200 patients with infectious diseases, such as diphtheria, scarlet fever, pertussis, and measles, a diagnosis of myocarditis was made on clinical grounds alone in 55 per cent and on electrocardiographic evidence alone in 24 per cent. The author considered the clinical signs to include pallor, listlessness, vomiting, albuminuria, cardiac enlargement, bradycardia, tachycardia, gallop rhythm and hypotension, with the principal sign a first heart sound of poor quality. He found the earliest electrocardiographic sign was a flattened T wave, which later became isoelectric and eventually inverted. Depression of the S-T segment and low voltage of the QRS complex often were present. The duration of myocarditis in his patients was from 2 weeks to 4 months. In 75 per cent of the subjects, its termination could be determined only by electrocardiograms.

Frequency of Myocarditis in Specific Infectious Diseases

Diphtheria. Myocarditis in diphtheria is well recognized as occurring frequently.

Streptococcal Infections. Recently, emphasis has been placed on scarlet fever as another common cause of myocarditis.[6] Two studies of acute beta-hemolytic streptococcal respiratory infections (Rantz and associates[7] and Watson, Rothbard, and Swift[8]) revealed that electrocardiographic changes of a transient nature often occurred during the height of the infection. The electrocardiogram became normal as the acute infection subsided; there was no relation to the late "phase III" illness which is indistinguishable from rheumatic fever. In the poststreptococcal state, Rantz,[9] in a recent report, advised caution in interpreting poststreptococcal myocarditis as different from rheumatic myocarditis. Similar findings were described by Gore and Saphir.[7]

Pneumonia. A number of reports on the incidence of myocarditis in pneumonia have appeared (Stone,[10] De Graff and associates,[11] Saphir,[12] Master and co-workers,[13] and Thomson and associates[14]).

Typhoid Fever. Serial clinical and electrocardiographic observations of myocarditis in typhoid fever were made by four groups of investigators, Thayer,[15] Brow,[16] Porter and Bloom,[17] and Rachmilewitz and Braun.[18] Their results indicated a higher incidence of myocarditis in this disease than had been suspected previously.

Meningococcic Meningitis. Saphir,[19] in a series of ten autopsies on patients who had died of meningococcal infection, found two instances of myocarditis caused by actual seeding of the organisms in the myocardium. Lowe and Diamond[20] reported a case of meningococcic meningitis in a 13 year old girl. During the disease, necrotic skin lesions, pericarditis, cardiac dilatation, heart failure, and peripheral edema developed. Characteristic electrocardiographic changes were noted. An operation was performed, during which lesions were seen on the pericardium. It was suggested that their course had paralleled that of the cutaneous lesions.

Tuberculosis. Wallgren[21] concluded that tuberculous heart disease is rare. In his opinion, pericarditis associated with this disease is often a tuberculous-allergic phenomenon. Auerbach and Guggenheim[22] in 10,165 autopsies on adult tuberculous patients found the myocardium involved in 0.28 per cent. In autopsies on 973 children, the incidence of myocarditis was found to be 3.9 per cent.

Mumps. Rosenberg[23] reported on 2 patients whose mumps were accompanied by complete heart block, and who developed precordial pain and faintness. Both patients recovered completely. Wendkos and Noll[24] studied 15 cases of mumps and found one instance of myocarditis as evidenced by transient partial A-V block and flat T waves.

Influenza. Hyman[25] reported 3 cases of heart block in influenza, but suggested that many cases were missed because of lack of electrocardiographic studies. Finland, Parker, Barnes,

and Joliffe[26] described 2 instances of death from influenza infections in which extreme degrees of diffuse myocarditis were seen at autopsy.

Atypical Pneumonia. Painton, Hicks, and Hartman[27] took electrocardiograms during the acute illness and convalescence of 63 patients with atypical pneumonia. While 12 subjects showed electrocardiographic evidence of myocardial and pericardial involvement, only 2 of the 12 presented clinical evidence of cardiac abnormality.

Infectious Hepatitis. Dehn, Feil, and Kinderknecht[28] studied 11 cases of infectious hepatitis during an epidemic. Electrocardiographic changes were minor and cleared during convalescence.

Infectious Mononucleosis. Evans and Graybiel[29] examined serial electrocardiograms in 100 cases of infectious mononucleosis; 4 proved cases were described in detail.

Measles. Degen[30] performed a series of autopsies on patients who had died from measles. In 91 hearts, he found 4 instances of cellular infiltrations in the myocardium, including 2 with exudative pericarditis.

Poliomyelitis. Gefter[31] studied 467 patients with poliomyelitis. Electrocardiograms taken on 226 of the 467 subjects showed abnormalities in 32 (14.2 per cent). Saphir and Wile[32] found an interstitial myocarditis with perivascular foci of lymphocytes in the hearts of 6 of 7 patients who had died of poliomyelitis. Dublin and Larson[33] found 2 instances of acute myocarditis at autopsy in 12 patients who had died of poliomyelitis. Peale and Lucchesi[34] demonstrated changes characteristic of myocarditis in the hearts of 7 of 9 patients dying of bulbar poliomyelitis. Two of the patients exhibited rapid, thready pulse and cyanosis before dying.

Epidemic Encephalitis. Ungar[35] reported a case of diffuse interstitial myocarditis in epidemic encephalitis. He concluded that myocarditis occurs during this disease more frequently than is realized.

Scrub Typhus. Säyen[36] found pathologic, clinical and electrocardiographic evidence of myocarditis in a series of persons with scrub typhus. All the patients who died showed extensive myocardial damage at autopsy. Sokolow and Garland[37] and Levine,[38] in follow-up studies of scrub typhus, concluded that the heart of a patient who survives the acute phase of the disease eventually shows complete return of function. In his monograph on typhus fever, Wolbach and associates[39] described the typical vascular lesions of the disease and demonstrated that such lesions were not uncommon in the myocardium. Woodward and Bland[40] studied 40 patients with typhus fever and concluded that peripheral rather than central circulatory collapse was the main clinical problem.

Subjects and Methods

An intensive study was made of 84 patients who were suffering from a wide variety of acute infectious diseases. Representative cases of varying severity were selected. Patients with pre-existing cardiac disease and those harboring beta-hemolytic streptococci in the throat, unless these organisms were considered to be the primary pathogenic agent, were excluded from the series.

A clinical evaluation of the cardiovascular system of each patient was made daily. It included determinations of temperature, pulse rate, arterial blood pressure, heart size, quality of the apical first heart sound, relationship of the intensity of the aortic and pulmonic second heart sounds, cardiac rhythm, and the presence of murmurs, gallop rhythm, distension of the neck veins, pulmonary abnormalities, cyanosis, edema, enlargement of the liver, and dyspnea. In most instances any significant clinical findings were checked by at least two of us.

Determination of circulation time and venous pressure was made every other day on patients old enough to cooperate. Alpha lobelin was used to determine the circulation time in comatose patients, magnesium sulfate and saccharin were used in all others. Venous pressure determinations were done with the zero level considered to be 5 cm. below the angle of Louis. A water-filled spinal fluid manometer attached to a three-way stopcock was used. A venous pressure greater than 12 cm. water and a circulation time greater than 12 seconds with alpha lobelin and 16 seconds with magnesium sulfate or saccharin were considered abnormal. Blood counts and sedimentation rates were done on each patient at entry and were repeated as indicated.

Electrocardiograms were taken on each patient from 1 to 24 hours after his entry to the hospital and, in most cases, were repeated every other day during his entry stay. Standard leads I, II, and III and unipolar leads aV_L, aV_F, V_1, V_3, and V_5 were used routinely. Other unipolar precordial leads were taken when indicated. Criteria for abnormality were as follows:

1. Diphasic or inverted T waves (except in rare instances where low to flat T waves were present

with tall R waves (an R/T ratio of greater than 10:1), provided they became normal on serial observation).

2. Abnormal contour of T waves which persisted in serial observations. (This phenomenon was always accompanied by other aberrations in the electrocardiogram.)

3. RS-T deviation greater than 0.5 mm. in Lead I and greater than 1.0 mm. in all other leads.

4. Complete atrioventricular dissociation, dropped beats, or a P-R interval over 0.21 second in adults or over the upper limits for age and rate in children as defined by Ashman and Hull.[41] In serial records, a change of 0.04 second or more in the P-R interval, unless the interval exceeded 0.20 second, was required.

5. Arrhythmias, such as nodal rhythm, ventricular ectopic beats at a heart rate greater than 120, auricular fibrillation, and other ectopic rhythms.

6. Intraventricular conduction defects where the QRS duration exceeded 0.11 second. The upper limits of Q-T interval were determined according to age and rate as defined by Ashman and Hull[41] using Bazett's formula.

A normal electrocardiogram of each patient, taken at some time during the course of his illness, was used as a control. Usually the electrocardiogram became normal during convalescence, although in some instances it was normal at the time of the first record and became abnormal later. No patient was included in the series unless a normal control observation was available.

Results

In the 84 cases accepted for evaluation, serial electrocardiograms were definitely abnormal in 28 patients (33 per cent), borderline in 5 (6 per cent), and normal in 51 (61 per cent) (table 1). Abnormal T waves were present in 20 patients, prolongation of the P-R interval in 8, significant RS-T deviation in 3, and abnormalities in rhythm in 6. Prolongation of the QRS interval was noted in only 4 patients. Figures 1, 2, 3, and 4 illustrate typical electrocardiographic changes found.

Abnormality of the T waves (table 2) proved the most frequent and sensitive indication of myocarditis. The use of unipolar leads was of considerable value in demonstrating this aberration. In 12 of the 20 patients manifesting abnormal T waves, the significant changes were shown in the unipolar limb or precordial leads, or both, whereas the standard leads showed either normal or borderline patterns. In only two instances where the T waves in standard Lead I were abnormal did the unipolar leads fail to reflect the change.

Alterations in the contour of the T waves were often significant. Many patients demonstrated flat-topped broad T waves which, in serial records, gradually became sharply peaked and normal in shape (fig. 3).

Table 1.—*Electrocardiographic Diagnoses in 84 Cases of Infectious Disease*

Disease	Total	Normal	Abnormal	Borderline
Diphtheria	16	8	8	0
Tuberculous meningitis	9	8	1	0
Typhoid fever	8	0	7	1
Measles	8	6	0	2
Infectious mononucleosis	7	7	0	0
Scarlet fever	6	3	2	1
Streptococcal pharyngitis	5	4	1	0
Lobar pneumonia	5	2	3	0
Meningococcal infections	5	2	3	0
Viral infections CNS unknown etiology	4	4	0	0
Pneumococcal meningitis	1	0	1	0
Influenzal meningitis	1	0	1	0
Streptococcal meningitis	1	0	0	1
Acute brucellosis	1	1	0	0
Poliomyelitis	1	1	0	0
Vincent's pharyngitis	1	1	0	0
Psittacosis	1	1	0	0
Chicken pox	1	1	0	0
Total	84	51 (60.8%)	28 (33.3%)	5 (5.9%)

The abnormalities in rhythm and conduction included bundle branch block, partial A-V block with and without dropped beats, complete A-V dissociation, and nodal rhythm with and without A-V block. With the exception of partial A-V block in several patients and dropped beats in a patient with mumps (fig. 4), these abnormalities in conduction and rhythm occurred only in the patients with diphtheritic myocarditis.

Abnormalities first appeared in the electrocardiograms from 1 to 19 days after the date of onset of the disease, with the majority occurring within the first 10 days. In scarlet fever abnormalities usually became apparent during the second and third weeks, presumably when toxicity was greatest.

Twenty-five patients were febrile and 3 were

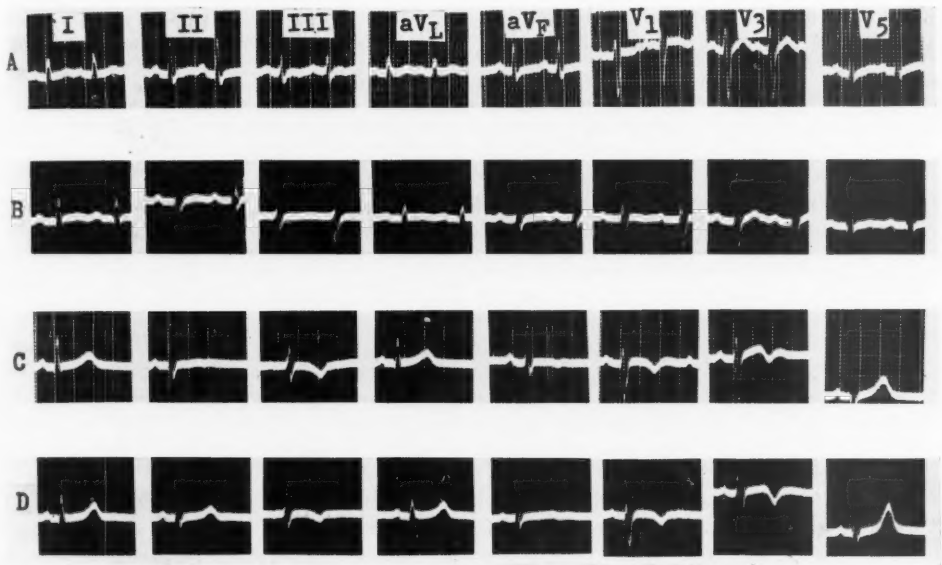

FIG. 1. D. P., female, age 11 years. Meningococcal meningitis. Onset Jan. 26, 1948. Illustrating partial A-V block and serial T-wave changes. *A*. Jan. 27, 1948. *B*. Jan. 30, 1948. *C*. Feb. 7, 1948. *D*. Feb. 17, 1948.

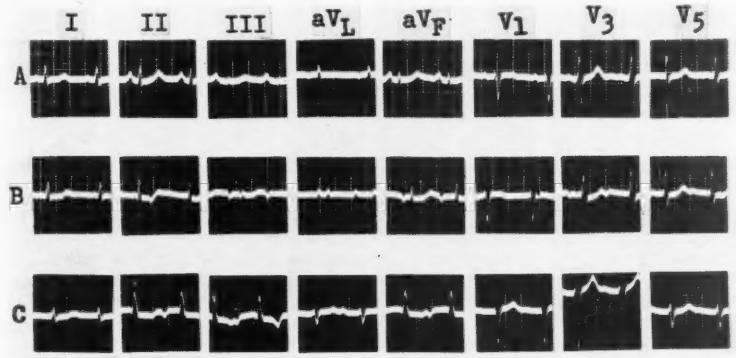

FIG. 2. E. D., male, age 48 years. Onset March 5, 1948. Illustrating serial changes in S-T segments and T waves, with appearance of nodal rhythm with A-V block. *A*. March 11, 1948. *B*. March 13, 1948. *C*. March 15, 1948.

and acute streptococcal sore throat, abnormal changes, if any, usually appeared within one to two days after onset and seldom persisted for more than a day or two. In typhoid fever, afebrile at the time the first abnormalities were seen in the electrocardiograms. In general, the abnormalities appeared in the electrocardiogram during the acute febrile phase of illness

and persisted for a short time into convalescence. Eventually, all the electrocardiograms became normal.

Clinical Manifestations of Myocarditis (Table 3)

Of the 28 patients with abnormal electrocardiograms, 13 (46 per cent) manifested an apical heart sound of poor quality. Of the 51 with normal electrocardiograms, only 2 patients (4 per cent) demonstrated a poor apical heart sound on serial examination. Both patients were comatose at this time and died shortly thereafter.

The poor quality of the first heart sound was first noted from 1 to 44 days after the onset of the infection. This sign persisted from 1 to 38 days. In the group with abnormal electrocardiograms, this auscultatory evidence did not vary more than 4 days in either direction from the first appearance of electrocardiographic abnormalities. In half the group, the muffled first heart sound and the appearance of electrocardiographic abnormalities were noted at the same time. Abnormal apical first heart sounds persisted for periods lasting from 8 days before to 40 days after the last abnormal changes were

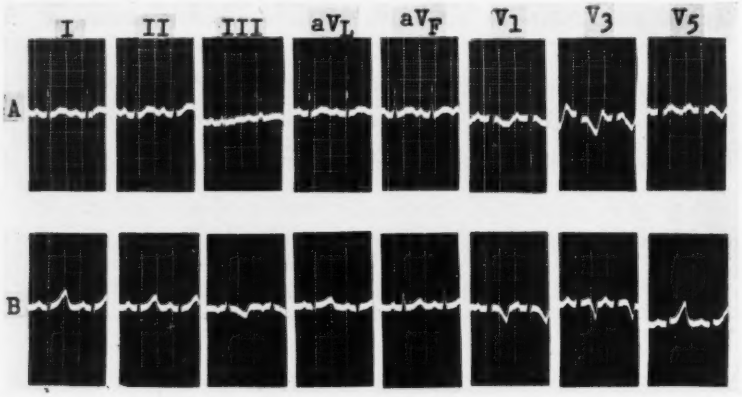

FIG. 3. G. R., male, age 2½ years. Typhoid. Onset November 25, 1947. Illustrating abnormality of T-wave contour. *A*. Dec. 11, 1947. *B*. Dec. 17, 1947.

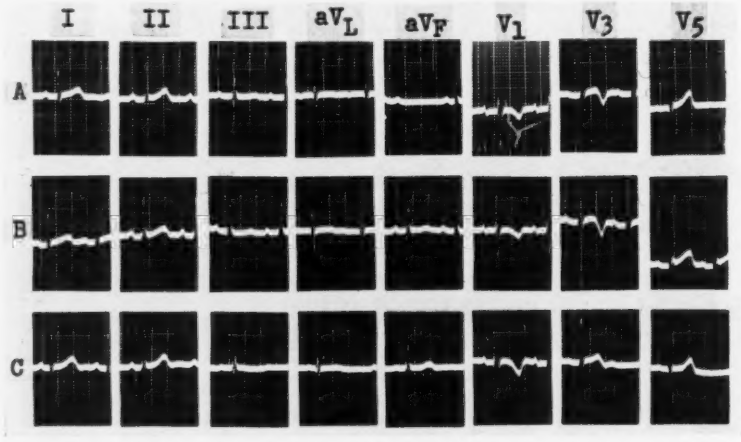

FIG. 4. M. S., female, age 5 years. Mumps. Onset March 9, 1948. Illustrating partial A-V block with dropped beats and serial changes in contour of the T waves in leads I, aV$_L$ and aV$_F$. *A*. March 15, 1948. *B*. March 17, 1948. *C*. March 29, 1948.

seen in the electrocardiogram. A first heart sound of poor quality, although difficult to describe, has a distinctive muffled, distant or weak quality. There was little disagreement among us as to when the apical first heart sound was of poor quality.

TABLE 2.—*T-Wave Abnormalities Found in 84 Cases of Infectious Disease*

	Low	Diphasic	Inverted	Total
T_1	4	1	6	6
T_2	5	3	10	10
T_{VL}		1	1	1
T_{VF}	1	1	8	8
T_{V3}	3	3	11	11
T_{V5}	5	2	12	12
Total	18	11	19	

abnormal rhythm was heard for only one day during the course of the disease.

Apical systolic murmurs of varying intensity were heard in 12 (43 per cent) of the patients with abnormal electrocardiograms. The murmurs were first noted from 9 days before to 5 days after the abnormalities were first apparent. In 5 of the 12 patients, their occurrence coincided with the appearance of the first aberrations in the electrocardiogram. The murmurs persisted from 1 to 60 days. They were last heard from 25 days before to 10 days after the last abnormalities were seen in the electrocardiogram, disappearing, in most cases, 2 to 3 days before or after this event. Of the 53 with normal electrocardiograms, 14 patients (26 per cent) developed murmurs.

Pulse rates greater than 125 per minute were

TABLE 3.—*Clinical Manifestations of Myocarditis in the Present Series of 84 Cases*

Clinical Manifestation	Total Number	Patients—Abnormal ECG.	Patients—Normal ECG.	% With Abnormal ECG.	% With Normal ECG.	Ratio % Abnormal to Normal
Poor quality M_1	15	13	2	46.6	3.7	~12:1
Drop in systolic blood pressure 20 mm. or more	11	8	3	28.6	6.0	~5:1
Gallop rhythm	12	8	4	28.5	7.2	~4:1
Systolic murmur	26	12	14	42.8	25.9	~2:1
Pulse rate greater than 125	22	11	11	39.3	21.6	~2:1

Of the group with abnormal electrocardiograms, 8 (29 per cent) showed a decrease in systolic blood pressure of 20 mm. or more, as compared to control convalescent blood pressure levels. Of the group with normal electrocardiograms, only 3 (6 per cent) had a comparable fall in blood pressure.

Of the 28 individuals with abnormal electrocardiograms, 8 (28.5 per cent) developed a diastolic gallop rhythm sometime during the course of the disease. In 6 of these patients, it was heard within four days after the first abnormalities appeared in the electrocardiogram; in 3, its onset coincided exactly with the date of their appearance. This sign was heard from 8 days before to 25 days after the last abnormalities were seen in the electrocardiogram; it persisted from 1 to 60 days. Of the 54 patients with normal electrocardiograms, only 4 (7 per cent) developed a gallop rhythm. In all 4, the

noted in 11 (39.3 per cent) of the group with abnormal electrocardiograms and in 11 (21.6 per cent) of the group with normal electrocardiographic patterns. This pulse rate was selected arbitrarily; it is apparent that under certain circumstances a pulse rate of 125 may be considered perfectly normal.

Thus, it may be concluded that an apical heart sound of poor quality is by far the most reliable clinical sign of myocarditis. The next most dependable signs are, in order of importance: a drop in systolic blood pressure of 20 mm. or more, gallop rhythm, systolic murmur, and a pulse rate greater than 125 per minute.

Table 4 summarizes the distribution of these clinical signs in the patients with abnormal electrocardiograms. Twenty-four of the 28 patients with myocarditis had at least one of the five clinical signs. Of these, 3 had an apical first heart sound of poor quality as a single

manifestation, 3 had systolic murmurs alone, and 2 had pulse rates greater than 125 alone. Six patients demonstrated both an apical heart sound of poor quality and gallop rhythm. Five patients had a combination of apical heart sound of poor quality, gallop rhythm and a murmur. In 2 patients, the venous pressure was elevated; in 3 patients, the circulation time was prolonged.

None of the patients with normal electrocardiograms developed elevated venous pressure or prolonged circulation time.

Table 4.—*Clinical Signs in 28 Patients with Abnormal Electrocardiograms*

Name	Age	Disease	Poor M_1	Drop in Systolic BP 20 mm. or More	Gallop Rhythm	Systolic Murmur	Pulse Rate More than 125 per Min.
D.P.	11	Meningococcemia	+	0	+	+	+
C.F.	7	Tbc. meningitis	+	0	+	+	+
A.N.	3½	Mening. meningitis	+	0	+	+	+
L.W.	2½	Typhoid fever	+	0	+	+	+
H.C.	7	Typhoid fever	+	+	+	0	+
J.H.	3	Typhoid fever	+	+	+	+	0
L.Y.	56	Typhoid fever	+	+	0	0	+
J.K.	9	Typhoid fever	0	+	+	0	0
B.J.	61	Strep. meningitis	0	+	0	+	0
L.B.Y.	10½	Scarlet fever	0	0	+	+	0
G.R.	2½	Typhoid fever	+	0	0	+	0
H.V.	?	Diphtheria	+	+	0	0	0
M.S.	5	Mumps	+	0	0	+	0
A.C.	32	Typhoid	0	0	0	+	+
J.H.	40	Diphtheria	0	+	0	0	+
J.S.	43	Pneumonia	0	+	0	0	+
J.M.	26	Scarlet fever	+	+	+	0	+
F.S.	51	Meningococcemia	0	0	0	+	0
L.M.	7½	Diphtheria	0	0	0	+	0
L.I.	31	Pneumo. meningitis	+	0	0	0	0
E.D.	48	Diphtheria	+	0	0	0	0
O.O.	49	Diphtheria	+	0	0	0	0
C.F.	37	Diphtheria	0	0	0	0	+
I.E.	33	Typhoid fever	0	0	0	0	+
D.P.	11	Scarlet fever	0	0	0	0	0
H.B.	42	Influ. meningitis	0	0	0	0	0
H.S	49	Pneumonia	0	0	0	0	0
J.S.	31	Strep. throat	0	0	0	0	0

Eleven of the patients studied died: 1 of post-measles encephalitis, 1 of *Staphylococcus aureus* lobar pneumonia, 1 of typhoid fever, 3 of diphtheria, and 5 of tuberculous meningitis.

The patient who died of post-measles encephalitis had T waves bordering on the abnormal. The patient with *Staphylococcus aureus* pneumonia had a normal electrocardiogram, although clinical signs pointed to congestive failure. Neither of these patients was autopsied. The patient with typhoid fever revealed myocarditis, both clinically and electrocardiographically, and at autopsy showed toxic degeneration of the muscle fibers and interstitial myocarditis (fig. 5). All 3 patients with diphtheria showed bizarre electrocardiographic abnormalities before death. The 2 who were examined at autopsy manifested definite toxic degenerative changes in the myocardium (fig. 6). One patient with tuberculous meningitis and miliary tuberculosis had clinical and electrocardiographic signs of myocarditis. Autopsy revealed only hyaline degeneration of some of the muscle fibers, which was thought to be toxic in origin (fig. 7). Of the remaining 4 patients with tuberculous meningitis, 2 had borderline electrocardiograms, one had abnormal clinical signs but no electrocardiographic aberrations, one was nor-

mal both by clinical and electrocardiographic evidence. These last 4 patients showed no evidence of myocarditis at autopsy.

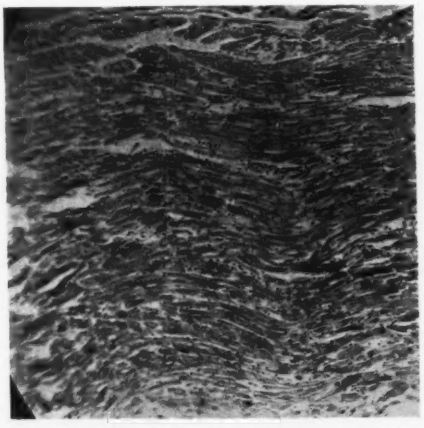

FIG. 5. Typhoid fever. Toxic degeneration of muscle fibers and interstitial myocarditis. (Hematoxylin and eosin × 100)

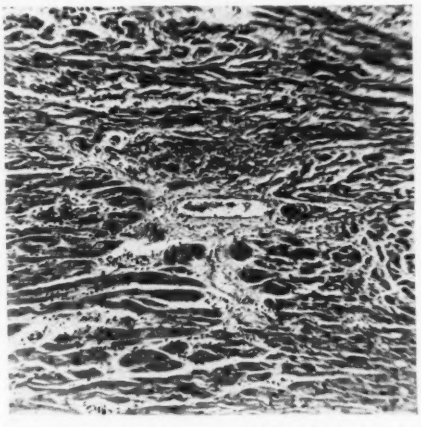

FIG. 6. Diphtheritic myocarditis. Marked toxic degeneration. (Hematoxylin and eosin × 100)

Effect of Artificial Fever Therapy on the Heart

As stated previously, most of our patients were febrile when the first abnormalities appeared in the electrocardiogram, but became afebrile before the electrocardiographic patterns returned to normal. In order to determine the effect of fever and tachycardia per se on the heart, we studied an additional 18 patients who were receiving artificial fever therapy. All subjects, according to history and physical examination, were free of pre-existing cardiac disease.

The 18 patients were kept at 105 to 106 F. by means of bakers and blankets for six hours. Each patient was given 500 cc. of 3 per cent sodium chloride intravenously immediately before therapy, and sedation as needed. Electrocardiographic, clinical and hemodynamic studies (the same described for the patients with acute infectious diseases) were made after each patient had one or two treatments. Control studies were made before therapy was begun and were repeated immediately after treatment, while the temperature was still at 106 degrees.

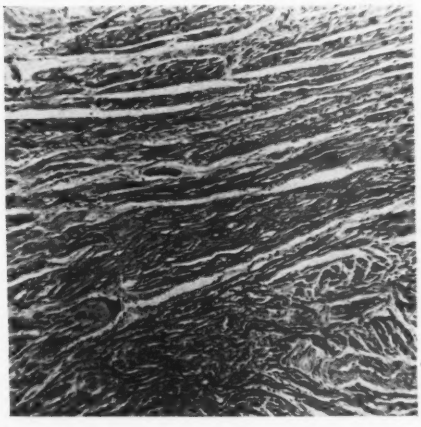

FIG. 7. Miliary tuberculosis and tuberculous meningitis illustrating "toxic" changes in the myocardium. (Hematoxylin and eosin × 100)

There have been several previous descriptions of the effect of fever on the electrocardiogram.[42–49] According to these reports, only an occasional patient receiving pyrotherapy showed significant electrocardiographic deviations; the majority demonstrated no electrocardiographic abnormalities.

The results of our study were in agreement with these observations. In the 18 patients studied, minor S-T deviation, usually depression, and a slight lowering of the R and T waves were fairly common. No clinical signs of cardiac disturbance were present, with one exception. One patient showed significant changes in the

electrocardiogram; the T wave in Lead II became diphasic and in aV_F became inverted. He seemed to be in a shocklike state and manifested tachycardia and hypotension. In this patient, the venous pressure rose from 4.5 cm. of water before therapy to 11.0 cm. after therapy. The circulation time increased from 16 to 21 seconds, whereas all the other patients showed a definite decrease. The pulse rate rose from 83 to 136 per minute; blood pressure fell from 140/90 to 96/54. Embryocardia and an apical first heart sound of poor quality were present.

Discussion

In diphtheria and scarlet fever, the myocardium probably is affected by toxins circulating in the blood stream. This also may be true in typhoid fever, acute streptococcal disease, bacterial pneumonia, and other infectious diseases characterized by toxemia.

In certain other infectious diseases, different elements may contribute to the derangement of myocardial function. A specific infection of the myocardium is known to occur in rare cases of tuberculosis and in pyemia from various causes. In benign virus deseases, such as mumps, influenza A, and measles, it is possible that the myocardium is directly attacked by the virus. Schmidt[50] isolated a virus from a chimpanzee dying of interstitial myocarditis which produced a myocarditis and encephalitis when injected in mice, hamsters, and guinea pigs. It could not be identified with any variety of known viruses.

It also is possible that electrolyte and fluid imbalance may contribute to the electrocardiographic changes characteristic of myocarditis. The acidosis and electrolyte imbalance of diabetic coma often results in electrocardiographic changes.[51] Barker, Shrader, and Ronzoni[52] studied the effects of alkalosis and acidosis in man as reflected in the electrocardiogram. Alkalosis was produced by hyperventilation and ingestion of sodium bicarbonate, and acidosis by ingestion of ammonium chloride. Alkalosis resulted in a definite reduction in the amplitude of the T waves, while acidosis caused a striking increase in their height.

Alterations of the serum potassium can lead to T wave, RS-T, and conduction abnormalities. Tarail,[53] in a report on a patient with uremia associated with hyperpotassemia, described peaked T waves of large amplitude and brief duration in Leads I and II, delayed intraventricular conduction, prolonged P-R interval, some tendency of the P waves to disappear, development of a deep Q in CF_2, abnormal S-T elevation, and an inclination to left ventricular strain. Other reports [54] have described the chief changes in hypopotassemia as low to flat T waves, depression of RS-T, and prolongation of the Q-T interval. Reduction of the ionized serum calcium produces typical changes with prolongation of the Q-T interval, sharply pointed positive T waves, and a long isoelectric course of S-T. Dehydration can cause flattening of the T waves and depression of the RS-T segments.[55]

Another hypothetic cause of myocarditis in infectious diseases might be an allergic factor similar to that presumed to produce rheumatic lesions. The presence of myocarditis early in the illness would militate against this possibility.

Rachmilewitz and Braun,[18] in a study of typhoid fever, gave two reasons for concluding that the abnormalities in the electrocardiograms of their patients were not due to myocarditis: (1) the pathologic changes in the heart were not sufficiently severe, (2) there was no clinical evidence of myocardial involvement. They gave 23 of their patients 300 to 600 mg. of niacin each day. The daily electrocardiogram returned to normal in 6 patients after two days, in 12 patients after three to five days, and in 4 patients after six to ten days. In 12 patients from whom niacin was withheld, the electrocardiographic patterns gradually improved, becoming completely normal in an average of $12\frac{1}{2}$ days.

Weiss and Wilkins[56] have shown that abnormalities in the T wave and the Q-T interval are common in conditions due to thiamin deficiency. Feil,[57] in a report on 38 patients with pellagra, found that approximately one-half showed sinus tachycardia, S-T segment abnormalities, inversion of the T waves, or prolongation of the Q-T interval.

Simonson, Henschel, and Keys[58] studied 32 young men who underwent 24 weeks of semistarvation. During this period, the electrocardiograms of the majority of subjects became abnormal and statistically, showed highly significant changes in the electrocardiographic components. The Q-T interval and the mechanical systole increased during semistarvation and shortened again during rehabilitation. The amplitude of all deflections (P wave, QRS complex, and T wave) decreased continuously and considerably during semistarvation and increased during rehabilitation. Most electrocardiographic components were back to control values within 32 weeks.

Our patients, in most instances, received two to three times the minimum daily requirement of all vitamins known to be essential to human nutrition (A, D, C, B, B_2 and niacin). Vitamin deficiencies probably contributed little, if any, to the abnormal findings.

Therapeutic agents also must be considered as a possible cause of myocarditis. One of our patients was excluded from the series when it became necessary to give him emetine for the treatment of amebic lung abscess. Many of our patients received sulfonamides. French and Weller[59] examined the hearts of 238 patients who had received sulfonamide drugs and found significant myocarditis in 126 (44.5 per cent). These workers gave therapeutic doses of sulfonamides to 60 mice and 47 rats, following which 38 of the mice and 33 of the rats developed interstitial myocarditis. McKinley[60] described a case of allergic carditis, pericarditis, and pleurisy during serum sickness. The electrocardiogram showed variable flat and negative T waves, with the major changes occurring after symptomatic recovery. Other observers[61] also have noted carditis in serum sickness. In our series, three patients with diphtheria developed serum sickness but showed no clinical or electrocardiographic evidence of carditis.

It is difficult to estimate the importance of myocarditis in infection. It is well known to be a cause of death in diphtheria. In most other fatal infections, since potentially lethal disturbances of systems other than the cardiovascular also are present, death appears to be due to a summation of many causes. The data of Saphir, Stone and others suggest that myocarditis is a common occurrence in patients dying of infectious diseases, but its presence does not mean that it is the most important cause of death. Our observations indicate that myocarditis rarely produces even a slight degree of congestive heart failure. Yet, sudden death from myocarditis may occur, although the usual picture of progressive heart failure is lacking. Thus, while many individuals dying of infectious diseases have myocarditis, most persons who develop myocarditis during an infectious disease survive. It is even unlikely that such acute myocarditis causes any important residual effects. The heart of every surviving patient in this series became normal, according to both clinical and electrocardiographic signs, before he was discharged from the hospital.

Summary and Conclusions

1. Serial clinical and electrocardiographic studies were made on 84 patients suffering from a variety of acute infectious diseases.

2. Of the patients, 33.3 per cent demonstrated electrocardiographic abnormalities as compared with their own normal control records. An additional 5.9 per cent manifested border-line electrocardiographic aberrations.

3. The majority of patients with abnormal electrocardiograms demonstrated clinical signs considered to represent myocarditis.

4. Physical findings generally associated with electrocardiographic abnormality were, in order of frequency: abnormality of the apical first heart sound, drop in systolic blood pressure of 20 mm. Hg, apical systolic murmurs, and a pulse rate greater than 125 per minute.

5. Myocarditis, as determined by clinical and electrocardiographic evidence, did not seem to be decisive in determining the survival of the patient, except in diphtheria. The patients in general were unaware of its presence.

6. Examples of myocarditis in typhoid fever, diphtheria and tuberculosis as determined at autopsy are presented.

7. The fever and tachycardia of pyrotherapy did not produce clinical or electrocardiographic signs of myocarditis in 17 of 18 patients who

were studied in the same manner as the 84 patients with infectious diseases.

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Therapy of Paroxysmal Pulmonary Edema by Antifoaming Agents

By Aldo A. Luisada, M.D.

Inhalation of certain volatile substances decreases the amount of foam in the respiratory passages and may be helpful in acute pulmonary edema. Experiments with several agents were performed in animals with different types of acute edema of the lungs. The best results were obtained with ethyl alcohol, which decreased the severity of the edema and prolonged the survival of the animals. Alcohol, while acting as an antifoaming agent, has no untoward side effects and is well tolerated. This method of therapy is now undergoing clinical tests.

IN SPITE of many accepted therapeutic measures, paroxysmal pulmonary edema still has a high mortality. Emergency treatment is complicated by the fact that some of the drugs which are useful in certain types of pulmonary edema might be detrimental in others. Morphine, barbiturates and chloral, advocated in cardiac patients[1, 2] are not advocated in pulmonary edema following injury to the central nervous system on account of their depressing action on the nerve centers. Intravenous strophanthin[3] might cause ectopic rhythms in pulmonary edema following coronary occlusion. Venesection, mercurial diuretics,[4] spinal anesthesia,[5] and possibly morphine[6] should not be used in pulmonary edema accompanied by shock because they further reduce venous return and cardiac output. Oxygen under pressure[7] may not be well tolerated by patients with emphysema. A new therapy which could be used in any case of paroxysmal pulmonary edema, irrespective of the cause, would be of great help and probably save many lives. For this reason, a new approach has been followed.

Part I. Studies on Pulmonary Edema Caused by Adrenaline

It has been known for a long time[8, 9] that fairly large amounts of fluid may be tolerated in the respiratory passages as long as no foam is formed. When the latter develops, increased volume of the air-fluid mixture and modified physical properties lead to severe effects by blocking the small bronchi. Anoxia then develops and is followed by higher pressure in the pulmonary artery[10] and increased transudation.[11] A vicious circle is then created which gradually increases the severity of the edema. When foam accumulates in the trachea, the effects are extreme and suffocation causes death. Therefore, the application of antifoaming agents was considered.*

Starting from this assumption, a systematic study was made in acute pulmonary edema induced by adrenaline in the rabbit, this being one of the easiest to produce and one of the most constant types of experimental pulmonary edema. The results of this study have been reported in a preliminary note.[12]

Material and Method

Adrenaline induces a fulminating type of pulmonary edema when injected intravenously in the rabbit, as proved long ago by Emerson.[13] It fails to do so in other species.

The study was made in a series of 109 white, male rabbits weighing between 1.5 and 2.5 kilograms. Paroxysmal pulmonary edema was induced by a standard method previously used by the author[1] and slightly modified by Glass,[14] namely by the injection of 2 cc. of a 1:1000 solution of adrenaline into the marginal vein of the ear, irrespective of the animal's weight. The injection time was kept as close to one minute as possible.

Twelve rabbits were used as controls, one or more

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* In vitro studies on antifoaming agents are being made by Epstein and co-workers.[20]

for each series of experiments. Only 1 out of 12 survived and presented no edema of the lungs.

Evaluation of the edema was done in the following way: (1) *Observation of the animal* for evidence of discharge of bloody foam from the nostrils or mouth. (2) *Survival time.* Usually, 50 per cent of the rabbits die within the first six minutes and nearly all within 30 minutes of the time of injection, as was confirmed by the controls in this particular batch of animals. If survival was longer, a maximum of 60 minutes was arbitrarily set, after which the animal was killed quickly, and the lungs examined. (3) *Appearance of the lungs.* When the lungs were removed, their gross appearance was noted and they were examined for the presence of foam in the trachea and on cut surfaces of the parenchyma. (4) *Weight of the lungs.* The lungs were weighed after removal of most of the trachea and of all other mediastinal organs. The lungs:body ratio was determined by dividing the weight of the lungs in grams by that of the animal in grams and multiplying the result by 100. Control studies on normal rabbits showed that, by this method, the average ratio is 0.45.

Inhalation of antifoaming agents was obtained in the following way. The rabbits were put into a box with a glass cover. The drug was sprayed at frequent intervals into the box through a hole, by means of an atomizer. Because the appearance of the pulmonary edema is abrupt, the animal was exposed to vapors of the antifoaming agent for ten minutes prior to injection of adrenaline, and after the injection until death, or for 60 minutes.

The following antifoaming agents were tested: ether, n-octyl alcohol* (octyl alcohol), methyl-n-hexacarbinol* (capryl alcohol), 95 per cent ethyl alcohol, and sorbitan triolate† (Span 85). None of these substances led to important general side effects. Ether and 95 per cent alcohol, after an initial period of excitement, caused mild sedation. The dose of ether and alcohol was kept below that causing anesthesia. Octyl and capryl alcohol seemed to cause some excitement in the animals.

In order to control the action of ethyl alcohol, this was also given intravenously in a subanesthetic dose (5 cc. per Kg. of a 25 per cent solution); by stomach or rectum in an anesthetic dose (8 to 10 cc. per Kg. of a 50 per cent solution); or with morphine sulfate. The latter was given in a dose of 10 mg. per Kg. by subcutaneous injection, as used in previous experiments of the author[1]; adrenaline was administered 30 to 40 minutes later.

Further control studies were made with morphine sulfate plus oxygen under pressure. Pure oxygen was given under a pressure of 30 to 40 mm. of water through a tracheal cannula in morphinized rabbits. Adrenaline was injected soon after starting the oxygen jet.

Results

The results of these experiments are summarized in table 1. *Span 85* did not change the severity of pulmonary congestion and edema; it abbreviated the survival time. The *heavy alcohols* (capryl and octyl alcohol) slightly increased the survival time and decreased the severity of the edema. *Ether* also had a mild beneficial action.

The action of *ethyl alcohol* by inhalation was far more marked than that of the other substances, as revealed by the fact that, after 6 minutes, 90 per cent of the animals were still alive; the average survival time was doubled; and the average lungs:body ratio was decreased from three times to twice the normal. This effect of ethyl alcohol was comparable to that of morphine.

Equivalent, subanesthetic doses of alcohol by intravenous injection had a less favorable effect. On the other hand, larger doses of alcohol, given by gavage or enema in sufficient amounts to induce a mild anesthesia, had a beneficial effect which was slightly superior to that of inhalation alcohol in a smaller dose.

Combined therapy was found to give the most beneficial results. Alcohol by inhalation associated with morphine by injection gave excellent results. This was comparable to that obtained by using oxygen under pressure associated with morphine by injection, as proved by the long survival time and the lack of edema.

Discussion

The stability of a foam is based upon the character of the air-fluid interface, namely on the surface tension of the fluid. Any substance capable of modifying the surface tension in such a way as to decrease the foam, is called an *antifoaming agent.* Some of these agents are oily, poorly volatile substances, like sorbitan triolate, and both capryl and octyl alcohol. Others, like ether and ethyl alcohol, are light and extremely volatile. This fact alone may influence their effectiveness, because penetration into the air passages and mixture with the foam is definitely more difficult with the former types than with the latter.

* Supplied by Eastman Kodak Co.

† Obtained through the courtesy of the Atlas Powder Co.

The unfavorable action of Span 85, which abbreviated the survival time, may be explained by the possibility that droplets of this oily substance were formed in the bronchi coating the mucosa and contributing to the obstruction of the air passages.

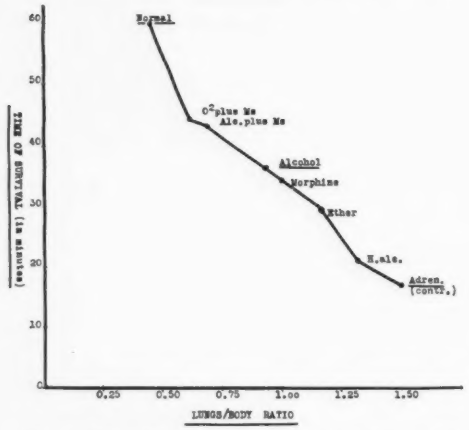

FIG. 1. The different action of several agents in adrenaline pulmonary edema is shown by a graph comparing the time of survival of the animals with the lungs:body ratio.

Heavy alcohols had a certain action on the foam revealed by the gross appearance of the cut lungs and by the scanty foam found in the trachea and bronchi. Still, the result was not remarkable, possibly because of toxicity and stimulation of the central nervous system.

Ether had a certain beneficial action. It is possible that congestion of the lungs and irritation of the bronchial mucosa somewhat counteracted the useful effect of decreasing the amount of foam.

Ethyl alcohol proved to be the best among the antifoaming agents. Controls with equivalent subanesthetic doses injected by vein and with larger anesthetic doses given via the gastrointestinal tract revealed that inhalation with alcohol is followed by two different effects. One is *local* and is due to the antifoaming property of this substance. The other is *general* and consists of depression of the nerve centers. The latter may result in peripheral vasodilation, decreased dyspnea, and other favorable effects similar to those obtained by other narcotics and anesthetics, as proved by the author in the same type of experimental pulmonary edema.[1]

The central action of alcohol explains only in part its useful effect by inhalation. This is proved by the fact that, in order to obtain comparable results, alcohol when administered parenterally has to be given in much larger doses than when it is inhaled. This shows that its antifoaming property is an important factor in the outcome.

TABLE 1.—*Influence of Various Antifoaming Agents on Adrenaline Pulmonary Edema of the Rabbit*

Drug	Per cent of Survival at LD/50* (6 min.)	Average Survival (min.)	Average Lungs: Body Ratio and Standard Error†	Per cent Developing Pulmonary Edema	Beneficial Effect	No. of Animals
(Normal Animals)	—	—	0.455 ± 0.021	—	—	4
Adrenaline (controls)	50	15.5	1.35 ± 0.035	92	—	12
Span 85	25	6	1.48 ± 0.094	100	o	4
Heavy alcohols (inhalation)	70	20.6	1.30 ± 0.098	90	x	10
Ether (inhalation)	100	29	1.15 ± 0.268	70	x	5
Morphine (subcutaneous)	90	35	1.01 ± 0.109	50	xx	10
Ethyl alcohol (inhal.) (subanesthetic dose)	90	35	0.95 ± 0.092	65	xx	20
Morphine (subcutaneous) plus ethyl cohol (inhal.)	100	42.4	0.68 ± 0.048	0	xxxx	10
Morphine (subcutaneous) plus oxygen under pressure	100	43.6	0.60 ± 0.051	0	xxxx	5

* One half the lethal dose.

† Standard Error $= \sqrt{\frac{\Sigma \Delta^2}{(n)(n-1)}}$

The useful action of inhaled alcohol is less apparent in the observation of the average results than in that of the single experiments. It should be kept in mind that adrenaline pulmonary edema is a fulminating syndrome which kills 92 per cent of the animals in 60 minutes and 50 per cent of them in 6 minutes. When treated with alcohol by inhalation, only 65 per cent of the animals had edema of the lungs; 35 per cent survived more than 60 minutes; and 90 per cent survived more than 6 minutes; only 1 out of 20 (5 per cent) discharged bloody foam from the nostrils. The useful action is even further demonstrated by the fact that it is equivalent to that of morphine sulfate.

The combination of parenteral morphine with alcohol by inhalation gave excellent results; all animals survived 6 minutes; 50 per cent survived 60 minutes; practically no edema of the lungs was found in any of the animals (table 1, figs. 1 and 2). The still existing mortality of a large percentage of rabbits is explained by toxic effect of the extremely large dose of adrenaline.

Statistical analysis was made of the data obtained in two series of experiments comparing alcohol by inhalation with alcohol by inhalation plus parenteral morphine. It was proved statistically that the means of lungs: body ratios in the two series are different and that the combination of the two drugs is superior to each of them alone (see table 1 and figs. 1 and 2).

As shown by previous studies, air and oxygen under pressure are effective in the treatment of adrenaline pulmonary edema of the rabbit.[7, 13] In our experiments, oxygen under pressure plus morphine saved a high percentage of animals. Comparison between this series and that of the animals treated by parenteral morphine plus alcohol by inhalation showed that the results obtained by using the two methods are equivalent.

The combination of the three remedies, morphine, oxygen under pressure, and alcohol vapor seems, therefore, to be indicated in many clinical cases, while oxygen under pressure and alcohol vapors, morphine being excluded, should be used in others.

Conclusions

Experiments were performed in rabbits with a series of antifoaming agents administered by inhalation in order to decrease the severity of pulmonary edema caused by a standard dose of intravenous adrenaline.

Poorly volatile drugs (heavy alcohols, Span 85) failed to exert any favorable effect. Ether gave only a slight benefit.

Ethyl alcohol exerted an important favorable action due to its antifoaming property; its action on the central nervous system, though slight on account of the dose used, may enhance the effect. The favorable effect of alcohol is comparable to that of morphine.

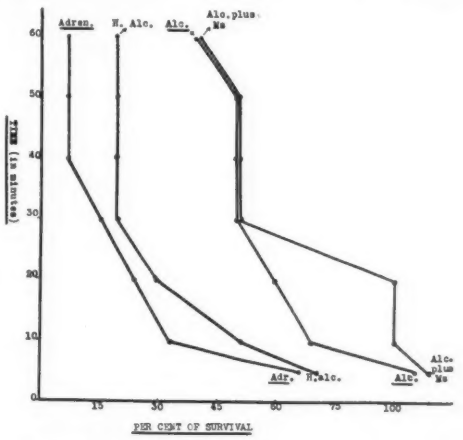

FIG. 2. The different action of several agents in adrenaline pulmonary edema is shown by comparing the various percentages of survival at subsequent intervals after the injection of adrenaline.

Combination of morphine by injection with alcohol by inhalation gave excellent results, equivalent to those obtained by morphine plus oxygen under pressure.

PART II. THE ACTION OF ALCOHOL IN SEVERAL TYPES OF EXPERIMENTAL PULMONARY EDEMA

A comparison of the action of several antifoaming agents was made by using as a standard method the acute pulmonary edema induced by adrenaline in the rabbit (part I). It was shown that ethyl alcohol by inhalation was the best, adding a mild general action (central sedation, possibly vasodilation) to a more im-

portant local action (antifoaming effect). Before suggesting clinical applications of this method, it was considered necessary to try the effect of alcohol vapor in several other types of pulmonary edema.

The following types of pulmonary edema were considered: (a) the edema caused in the rat by an intraperitoneal injection of thiourea, described by MacKenzie and MacKenzie[15]; (b) the edema caused in the guinea pig by ingestion of ammonium chloride, described by Koenig and Koenig[16, 17]; (c) the edema caused by the rapid intracarotid infusion of physiologic salt solution, described by Luisada and Sarnoff[18] in the dog and confirmed by Cheng[19] in the rabbit.

Technic

Thiourea was injected by MacKenzie and MacKenzie[15] in the adult rat (250–300 Gm.) by intraperitoneal injection in doses of 200 mg. per Kg. Pulmonary edema occurred in general within 16 to 24 hours, but sometimes earlier, within five hours.

In our experiments, white, adult rats weighing between 250 and 350 Gm. were used. Thiourea was used in a 10 per cent solution and 250 mg. per Kg. was the dose employed in the entire series of animals. Five of them were kept as controls; the other 5 were placed in a box containing a jar of alcohol-soaked gauze which evaporated readily, and were left there until death or for 22 hours. After this interval the surviving rats were killed and their lungs were examined.

Ammonium chloride was used by Koenig and Koenig[16, 17] to induce pulmonary edema in the guinea pig in the following doses: by intraperitoneal injection, 50 to 70 mg. per 100 Gm. of body weight; by gavage, 90 to 120 mg. per 100 Gm. of body weight.

A 10 per cent solution of ammonium chloride was made. In a first series of animals, 60 mg. per 100 Gm. of body weight were injected into the peritoneal cavity. In a second series, 100 to 120 mg. per 100 Gm. of body weight were given by gavage. Alcohol inhalation was obtained by placing the guinea pigs in a box into which alcohol was sprayed at frequent intervals. If the animals survived, they were killed after 60 minutes and their lungs were inspected and weighed.

The method of rapid injection of physiologic salt solution into the carotid arteries toward the brain was described by the author with Sarnoff.[18] The same technic was used in the present experiments: anesthesia with a small dose of morphine (3 mg/Kg. subcutaneously) and urethane (1 Gm./Kg. by gavage); intracarotid infusion under a pressure of 280 to 300 mm. Hg. Three infusions were given: the first, equivalent to 85 per cent of the blood volume; the second, to 80 per cent, 10 minutes later; and the third, equivalent to 65 per cent, 5 minutes later. The total infusion amounted to 2.3 times the blood volume, the latter being estimated as 10 per cent of the body weight. As a modification of technic, tracheotomy was performed in all our animals. Several squares of gauze were put into a flask partly filled with 95 per cent alcohol. The tubes from the tracheal cannula were suspended in the air chamber of the flask, and the top of this was lightly covered with alcohol-soaked gauze. The alcohol rapidly evaporating in the flask was thus inhaled. If the animal survived the procedure, it was killed 7 minutes after the end of the third infusion and the lungs were removed, inspected and weighed.

Discussion

Previous experiments showed the good results of alcohol administered by inhalation in the acute pulmonary edema of the rabbit and its superiority over other antifoaming agents. Present experiments dealt only with the use of alcohol in other types of experimental pulmonary edema.

Pulmonary edema caused by thiourea in the rat, as described by MacKenzie and MacKenzie[15] did not seem to be constant, because only 1 out of 5 controls developed the syndrome within 22 hours. Moreover, its late appearance made a therapeutic study more difficult. For this reason, the method was abandoned.

Pulmonary edema caused by ammonium chloride in the guinea pig, as described by Koenig and Koenig[16, 17] was not constant when

the drug was injected. It always resulted in death of the animals within a half hour when the drug was ingested (average survival time: 28.7 minutes). Postmortem study revealed a practically constant and severe lesion of the lungs consisting of hemorrhage, congestion and edema and a lungs:body ratio over twice that of normal animals. Treatment with alcohol vapor did not change the lungs:body ratio (table 2) although no foam was found in the bronchi or on the cut surface of the lungs in a large percentage of animals (50 per cent). On the other hand, 80 per cent of the animals were still alive after 30 minutes (20 per cent only of the controls) and 50 per cent were alive after 60 minutes (none of the controls). The average survival time was raised, therefore, from 28.7 minutes (controls) to 47 minutes. For these reasons, treatment with alcohol was considered fairly successful in pulmonary edema produced by ammonium chloride.

Acute pulmonary edema caused by rapid intracarotid infusion of physiologic salt solution is an invariably lethal procedure[18] and edema of the lungs is constantly caused by this method. Three control animals presented a lungs:body ratio of 5.62 indicating that their lungs were about six times heavier than the normal lungs. Foam poured abundantly out of the trachea and from the cut surface of the lungs. Four animals were submitted to alcohol inhalation, None of them presented edema of the lungs (table 3). Their average lungs:body ratio was 1.25 indicating merely an increased content of blood in the pulmonary vessels and no edema, as proven by Luisada and Sarnoff.[18] Therefore, the result of the above experiments was highly successful and further proved the efficacy of alcohol as an antifoaming agent.

Conclusions

Experiments were performed in three types of experimental pulmonary edema in order to test further the action of alcohol by inhalation.

Pulmonary edema caused by thiourea in the rat was found to be inconstant. This method of producing pulmonary edema was abandoned.

TABLE 3.—*Acute Pulmonary Edema in Dogs Caused by Rapid Intracarotid Infusion of Physiologic Salt Solution*

	Average Lungs: Body Ratio	Beneficial Action	No. of Animals
Normal dogs	0.80	—	4
Controls	5.62	—	3
Treated with Alcohol	1.25	xxxx	4

TABLE 2.—*Ammonium Chloride Pulmonary Edema in Guinea Pigs*

	Per cent of Survival		Average Survival in Minutes	Average Lungs: Body Ratio	Per cent Developing Pulmonary Edema	No. of Animals
	30 min.	60 min.				
Normal animals	—	—	—	0.91	—	4
Controls	20	0	28.7	1.87	80	10
Treated with Alcohol	80	50	47	1.85	50	10

Pulmonary edema caused in the guinea pig by ingestion of ammonium chloride did lend itself to a therapeutic study. Inhalation of alcohol vapor did not change the average lungs: body ratio. However, it decreased the percentage of animals developing pulmonary edema and improved remarkably the survival time of the animals.

Pulmonary edema caused by rapid intracarotid infusion of physiologic salt solution in the dog can be used only for study of the lungs, as the animals are sacrificed soon after the end of the experiment. Inhalation of alcohol vapors, tried on 4 animals, gave a striking result, entirely preventing the development of pulmonary edema.

Clinical Application

The favorable action of alcohol by inhalation in experimental pulmonary edema suggested its clinical trial in patients with this syndrome.

A preliminary study indicated the tolerance for inhaled alcohol vapor by normal subjects and cardiac patients; it also showed that the amount of alcohol absorbed through the mucosa of the respiratory passages is moderate and inadequate to induce anesthesia. Clinical treatment with alcohol by inhalation is now being tried at Mount Sinai Hospital. A report of the results will be made upon collection of sufficient evidence.

Summary

Experiments were performed in rabbits in which a series of antifoaming agents were administered by inhalation in order to decrease the severity of pulmonary edema caused by a standard dose of intravenous adrenaline. Poorly volatile drugs (heavy alcohols, Span 85) failed to exert any favorable effect. Ether gave only a slight benefit.

Ethyl alcohol exerted an important favorable action, due to the antifoaming property of alcohol; its action on the central nervous system, though slight because of the small dose used, may have enhanced the effect. The favorable effect of alcohol was comparable to that of morphine. Combination of morphine by injection with alcohol by inhalation gave excellent results, equivalent to those obtained by morphine plus oxygen under pressure.

Experiments were further performed in three other types of experimental pulmonary edema in order to test further the action of alcohol by inhalation.

Pulmonary edema caused by thiourea in the rat was found inconstant and the method was abandoned. Pulmonary edema caused in the guinea pig by ingestion of ammonium chloride proved to lend itself to a therapeutic study. Inhalation of alcohol vapor did not change the average lungs:body ratio. However, this therapy decreased the percentage of animals developing pulmonary edema and improved remarkably the survival time of the animals.

Pulmonary edema caused by rapid intracarotid infusion of physiologic salt solution in the dog can be used only for study of the lungs, as the animals are sacrificed soon after the end of the experiment. Inhalation of alcohol vapor, tried in four animals, gave striking results, entirely preventing the development of pulmonary edema.

Clinical treatment with alcohol by inhalation is now being tried and the results will be reported at a later date.

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Congenital Aortic Septal Defect with Communication between Aorta and Pulmonary Artery

Case Report and Review of Literature

By HERTA SPENCER, M.D., AND HARVEY J. DWORKEN, M.D.

A case of congenital defect of the aortic septum is reported, together with a summary of thirteen previously described cases. The authors briefly describe their concept of the dynamics of the lesion and suggest a method of possible surgical correction, in instances where the diagnosis is made early.

RECENTLY we have had the opportunity of examining a patient with a congenital defect between the base of the aorta and the pulmonary artery. A careful review of previous reports since the early 1800s revealed only 13 other proved instances of the anomaly, 10 of which were tabulated by Maude Abbott[1] in her extensive monograph on congenital heart disease. As in our patient, the correct anatomic diagnosis was not made in any instance prior to postmortem examination.

CASE REPORT

G. W., an 18 year old white male, was admitted to Mount Sinai Hospital on December 20, 1949 complaining of extreme shortness of breath, orthopnea, and increasing weakness during the previous five weeks. Marked dyspnea first appeared while the patient was walking leisurely, and readily disappeared with rest.

From his father, it was learned that the patient, an only child, was born with "a leakage of the heart" and a hare lip. However, his general development had been normal and, until recently, he had been able to exercise moderately and had never been cyanotic.

There was no history of rheumatic fever except for one episode in 1947, consisting of pain in both legs. This lasted for nine days, but fever or joint swelling did not appear.

The only x-ray film of the chest ever taken was during the Cleveland Tuberculosis Survey in April, 1949 (fig. 1). This showed an elongated chest with increased radiolucency of both lungs, indicating emphysema. The cardiothoracic ratio was 17.8:26.7 cm. The left ventricle was enlarged, extending to the extreme left of the chest, and the right heart border was moderately enlarged. The pulmonary artery and hilar vessels were prominent, and the aorta was slightly dilated.

On examination, the patient appeared undernourished, pale, severely orthopneic and moderately cyanotic. Temperature was 99.2 F., pulse 92 and grossly irregular, respirations 30, blood pressure 130/70. There was a hare lip deformity on the left, contiguous with a complete cleft palate. Neck veins showed marked engorgement. The thorax was increased in anteroposterior diameter, the left chest being more prominent than the right. There were diminished breath sounds and rales at both lung bases.

Precordial activity was marked, and a systolic thrill was felt, most intense in the third left intercostal space adjacent to the sternum. The left cardiac border was in the seventh intercostal space at the posterior axillary line. The rhythm was completely irregular, and a grade IV systolic murmur was present, loudest in the third left intercostal space adjacent to the sternum. The presence of a diastolic murmur in this area was debatable. Peripheral pulses were collapsing.

The abdomen showed a definite fluid wave. The liver edge was felt four fingerbreadths below the costal margin. Marked edema of the scrotum and lower extremities was present. Digital clubbing was absent.

The urine showed a trace of albumin and a few red and white cells in the sediment. Hemoglobin was 15.3 Gm., red blood cell count 5.8 million, white cell count 13,700. The nonprotein nitrogen was 130 mg. per 100 cc, the carbon dioxide combining power 25.8 volumes per cent. Kline test and a blood culture were negative.

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Read before a meeting of the Scientific Council of the Cleveland Heart Society on March 21, 1950.

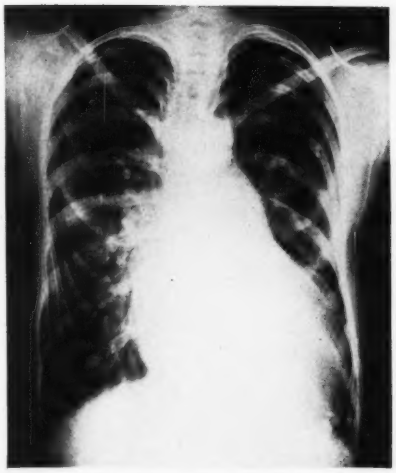

FIG. 1. Chest x-ray. See description in text.

varying from 0.14 to 0.16 second. The pattern was not specific for any type of bundle branch block.

The patient was in extremis and did not respond to diuretic or digitalis therapy. He expired 21 hours after admission. Because of the short hospital course, it was impossible to do complete diagnostic studies. Clinical diagnoses were: severe congestive heart failure, probably due to congenital heart disease, possibly a patent ductus arteriosus; possible chronic rheumatic heart disease; advanced pulmonary emphysema; terminal uremia.

At *autopsy* there was evidence of marked congestive failure, with massive peripheral edema and ascites amounting to 2 liters. The heart was markedly enlarged, weighing 960 Gm. The anterior surface was occupied chiefly by the right heart. Both ventricles were hypertrophied and of approximately equal thickness, the left measuring 16 mm., the right 15 mm. maximally. There was a large, round defect in the aorta (fig. 3), 12 mm. above the semilunar cusps. This opening was 20 mm. in diameter,

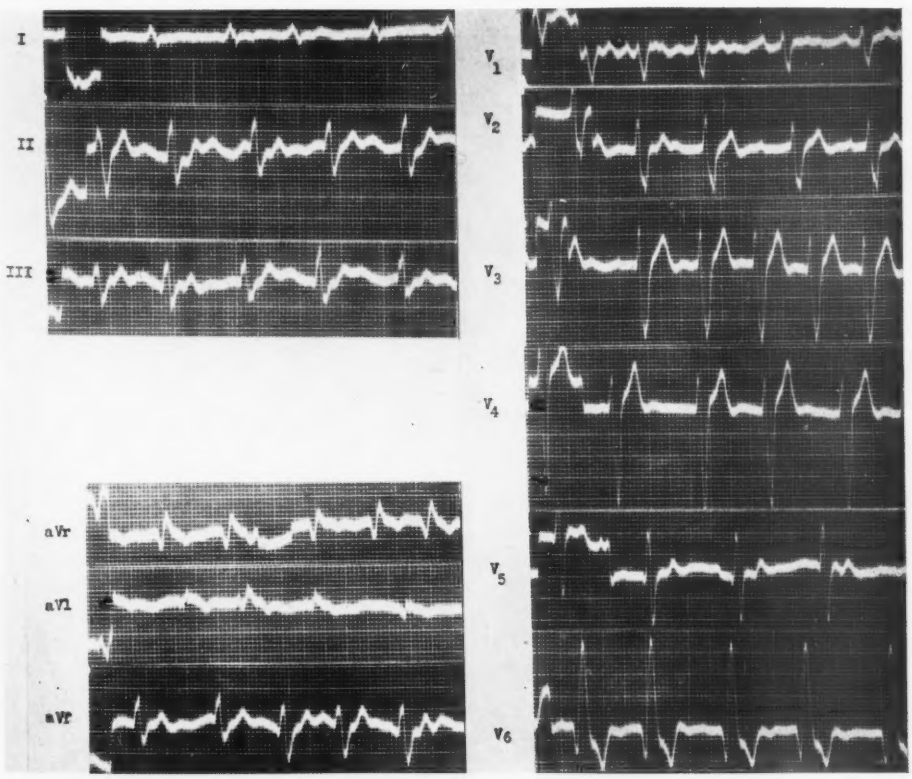

FIG. 2. Electrocardiogram. See description in text.

An electrocardiogram (fig. 2) showed auricular fibrillation, tall complexes throughout and a QRS had smooth edges, and led directly into the pulmonary artery. The aorta and pulmonary artery were densely adherent and could not be dissected apart. The pulmonary artery was wider than the

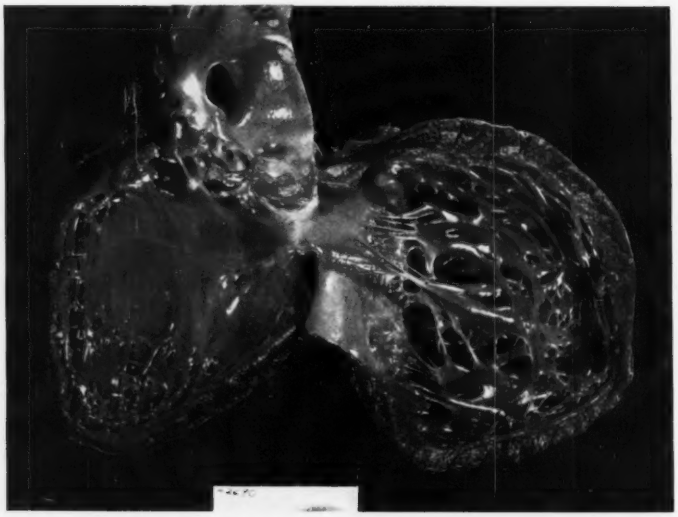

FIG. 3. Left ventricle, showing aorta with defect 12 mm. above the aortic valve.

(The use of color in this illustration has been made possible by a grant from Wyeth Incorporated to the publication fund of the American Heart Association.)

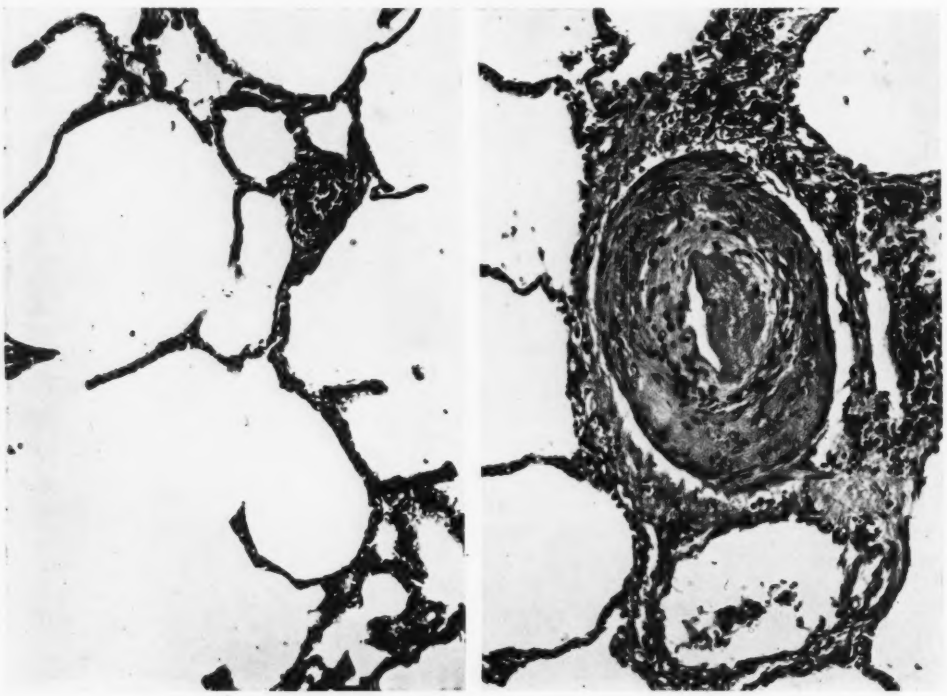

FIG. 4 (*Left*). Section of lung showing advanced emphysema. (×85)

FIG. 5 (*Right*). Marked thickening of the wall of a small pulmonary artery. (×85)

aorta and measured 8 cm. in circumference, the aorta 6.5 cm. at the base. There was no aortic disease, nor were any other cardiac anomalies noted. The edges of the aortic and pulmonic valves were somewhat thickened and slightly red. The mitral valve leaflets showed rolling and thickening of the edges and there was shortening of the chordae tendineae, suggestive of an old rheumatic process. Neither the ductus arteriosus nor the ligamentum arteriosum could be identified.

The lungs showed abnormal lobulation and were distended and voluminous throughout. The liver weighed 1560 Gm. and showed marked passive congestion. The spleen was enlarged and congested to the extent of the appearance of multiple hemorrhages within the pulp.

Microscopic findings showed hypertrophy of the heart muscle; section through the septal defect showed no evidence of disease. Severe, generalized pulmonary emphysema was present (fig. 4), and the smaller pulmonary arteries and arterioles showed striking sclerotic changes with narrowing of the lumina (fig. 5). In other areas, there was chronic passive congestion evidenced by the presence of heart failure cells and thickened alveolar septa.

Discussion

Thirteen cases of localized congenital defects of the aortic septum have been reported previous to the present.[1–14] Analysis of table 1 shows the age, sex incidence, size of defect, types of murmur and cause of death in these patients.

The aorticopulmonary communication is due to a partial defect in the development of the aortic septum, which under normal conditions completely divides the truncus arteriosus into the two great vessels by the seventh or eighth week of intrauterine life.[15] Usually, it is a round, smooth-edged defect in the anterior wall of the aorta, a short distance above the semilunar valves.

Aortic septal defects are to be differentiated pathologically from a shortened patent ductus arteriosus with approximation of the aorta and pulmonary artery, and the acquired type of communication caused by rupture of an aortic aneurysm into the pulmonary artery. In a shortened ductus, the lesion occurs beyond the origin of the left subclavian artery, while aortic septal defects appear just above the semilunar valves. Both lesions were present in Hektoen's case.[11]

Table 1.—*Tabulation of All Cases of Aortic Septal Defect Reported in the Literature, Including the Present Case*

No.	Author	Age	Sex	Murmurs		Defect in mm.	Associated Anomalies	Cause of Death
				Systolic	Diastolic			
1	Elliotson	Infant	F	?	?	10	None	Congestive heart failure.
2	Wilks	8 mos.	F	+	−	5	Patent foramen ovale.	Congestive heart failure.
3	Fraentzel	25 yrs.	F	+	+	12	Right pulmonary artery originated from aorta.	Congestive heart failure.
4	Gerhardt	5 mos.	F	?	?	5	None	?
5	Rauchfuss	Infant	?	?	?	?	?	Congestive heart failure.
6	Baginsky	4 yrs.	F	+	+	10	None	Pertussis, convulsions.
7	Caesar	9 yrs.	M	−	−	10	Perforated pulmonary cusps.	TBC-meningitis. Brain abcess.
8	Girard	27 yrs.	M	+	−	10	None	Congestive heart failure.
9	Rickards	30 yrs.	M	+	+	10	Bicuspid aortic valve. Interventricular septal defect.	Congestive heart failure.
10	Hektoen	Infant	M	?	?	15	Patent Ductus Arteriosus.	Congestive heart failure.
11	Moorhead & Smith	48 yrs.	M	+	+	10	None	Congestive heart failure.
12	Dadds & Hoyle	14 yrs.	M	+	+	60	None	Congestive heart failure.
13	Erf et al.	20 yrs.	M	+	−	32	Pulmonary Hemangioma.	Ruptd. pulmonary hemangioma.
14	Spencer & Dworken	18 yrs.	M	+	?	20	Cleft palate. Hare lip.	Congestive heart failure.

Schattenberg and Harris[17] state that three per cent of all ruptured syphilitic aortic aneurysms open into the pulmonary artery. They differ from congenital defects in that they have irregular edges and are situated higher in the aorta.[17–19] Aneurysms of the sinus of Valsalva almost invariably rupture into the right heart, and are easily differentiated from aortic septal defects.[16]

The cardiac history dating back to infancy, the associated malformations elsewhere in the body, and the fact that the aorta and pulmonary artery could not be dissected apart, all favor a congenital origin of the defect in the present case. The smooth edges on the opening and the absence of disease in the aorta indicate that it had not formed on an inflammatory basis.

The communication in aortic septal defects leads to circulatory changes similar to those seen in patent ductus arteriosus.[20] Because of the high pressure differential, oxygenated blood flows from the aorta into the pulmonary artery. This additional flow, estimated by Eppinger, Burwell and Gross [21] to be almost 50 per cent of the total output of the left ventricle, causes pulmonary hypertension, dilatation of the pulmonary artery, and eventually leads to left ventricular hypertrophy.

The right ventricular hypertrophy is a direct result of the prolonged pulmonary hypertension, which in turn was probably caused by a combination of factors: the arteriovenous shunt, the severe pulmonary emphysema and associated vascular sclerosis, and the marked congestive heart failure terminally.[21–23]

The terminal cyanosis in the present case was probably due to a reversal of the arteriovenous shunt associated with congestive failure, and the advanced emphysema. The abnormal pulmonary lobulations found suggest that the emphysema had formed on a congenital basis. The marked arteriosclerosis in the lungs may have been due to pulmonary hypertension, since Parker[24] found that 80 per cent of his patients with emphysema had this and ascribed it to the high pulmonary pressure in that disease.

Auricular fibrillation is rare in congenital heart diseases other than auricular septal defects or types associated with valvular disease.[25] Changes of the auricular wall, anoxia or other metabolic factors may have accounted for the fibrillation in our case. Cardiac arrhythmia has been reported in only one other case of aortic septal defect.[7]

Since angiocardiography has proved its value as an aid in the specific diagnosis of certain types of congenital heart disease, it may also be useful in confirming the presence of an aortic septal defect. Burford[26] has introduced the retrograde arterial technic which enables one to demonstrate a patent ductus together with the aorta and pulmonary artery, and this method could conceivably outline other aortic anomalies as well. According to Cournand,[27] such a method is essential in distinguishing a patent ductus from an aortic septal defect, since this cannot be done by cardiac catheterization alone.

In view of the present success of cardiac surgery, it is possible that aortic septal defects may be relieved by operation. Due to the fusion of the aorta and pulmonary artery, the communication could not be ligated in the manner of a patent ductus. A technically difficult procedure involving removal of the lesion and separately suturing the wall of the aorta and the pulmonary artery would be necessary.

Summary

The physical and pathologic findings in a case of aortic septal defect are described. A careful review of the literature revealed that only 13 similar cases have been reported previously. An attempt is made to outline clinical and laboratory methods which may prove of value in the differential diagnosis of this condition. Suggestions are made for accomplishing possible surgical correction of the defect.

Acknowledgment

We are grateful to Dr. Harold Feil, former chief of the Department of Medicine, and Dr. Benjamin S. Kline, chief of the Department of Laboratories for their advice in the preparation of this paper. We wish also to thank Mr. William Stevenson and Mr. Robert Newhouse for the photographs.

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Stokes-Adams Attacks Induced by Rectal Stimulation in a Patient with Complete Heart Block

By Roy W. Scott, M.D., and Salvatore M. Sancetta, M.D.

This paper reports a case of complete heart block whose Stokes-Adams attacks were induced by straining at stool and invariably by digital stimulation of the rectum. Electrocardiograms during attacks exhibited high ventricular tachycardia or fibrillation and chaotic heart action.

IN 1941, Parkinson, Papp and Evans[1] reported their observations on the electrocardiogram of the Stokes-Adams attack. Contrary to the prevailing view at the time that ventricular standstill is the only common disturbance in the cardiac mechanism which, occurring in patients with complete heart block, causes the loss of consciousness, they found that in one-third of the reported cases, including 8 of their own, unconsciousness was ushered in by a high ventricular tachycardia and/or fibrillation. Following is the report of such a case observed during spontaneous attacks and in whom the attacks were often induced by straining at stool and always by rectal stimulation with the gloved finger.

Report of Case

A white woman aged 62 was admitted to the hospital on August 3, 1944, and died during sleep nine days later. She had been in good health until two weeks prior to admission, when she suddenly collapsed and remained unconscious for several minutes. Many attacks of faintness with a few followed by complete loss of consciousness occurred daily until death.

Physical examination as well as the usual laboratory procedures were within the limits of normal other than the cardiovascular system. Between attacks the patient did not appear ill. The ocular fundi were the seat of grade 1 sclerosis. The heart sounds were normal and the rate about 42 with a slight irregularity in rhythm. The peripheral vessels were sclerotic, and the patient's general demeanor suggested some degree of cerebral arteriosclerosis. The blood pressure was 140/85. The electrocardiogram on admission showed almost complete auriculoventricular block, auricular rate 104, ventricular rate 52 (fig. 1).

Attacks of complete unconsciousness would be ushered in by a sudden irregularity and increase in rate of the pulse. The patient would then complain of shortness of breath and faintness. Suddenly the radial pulse would disappear and the heart sounds become inaudible. Breathing became stertorous, there were clonic convulsions together with dilatation of the pupils, followed by twitching of face muscles and spasmodic movements of the arms and legs. The face became cyanotic. The entire episode varied in duration from one-half to three minutes. With a return of the pulse, the attack ended abruptly, and the patient appeared little the worse for the experience.

After several days the patient observed that most of her attacks occurred while using the bedpan. To check this observation, a finger was inserted into the anal orifice and within a few seconds the patient became unconscious, exhibiting the picture just described. This attack lasted approximately two minutes.

The patient was moved to the electrocardiograph laboratory and a control record (fig. 2) was taken, which showed almost complete auriculoventricular block, auricular rate 92, ventricular rate variable, with ventricular beats multifocal in origin. In spite of the disturbance in the cardiac mechanism exhibited in figure 2, the patient during this time was conscious and unaware of the cardiac disorder.

A finger was now inserted into the anal orifice and the pulse stopped, but instead of ventricular standstill as we had anticipated, there ensued a rapid ventricular activity suggestive of an impure form of ventricular tachycardia or a coarse ventricular fibrillation with a ventricular rate in some instances over 300 per minute, as shown in strip 3 of figure 3. The onset and offset of a spontaneous attack associated with a brief period of unconsciousness is shown in figure 4.

After this observation was made, ephedrine was discontinued and quinidine started. Although spontaneous Stokes-Adams attacks lessened somewhat

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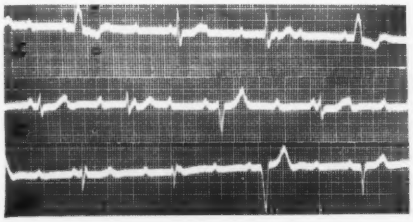

FIG. 1. Admission electrocardiogram showing 3 standard limb leads. Auricular rate is fairly constant at 104, ventricular rate is slightly inconstant at approximately 52. Record is interpreted as representing almost complete heart block, with the large, broad QRS complexes representing the dominant idioventricular pacemaker. The second QRS in Lead I is probably conducted. The second QRS in Lead III is nodal with retrograde P. Patient was asymptomatic at this time.

in severity and duration, the patient died 12 hours later.

At postmortem examination the heart weighed 300 grams. Grossly there was only slight coronary artery sclerosis and no areas of fibrosis were seen. On microscopic examination of the region of the common bundle a few foci of round cell infiltration were present. There was slight atrophy, fibrosis and vacuolization of the myocardial cells, and moderate arteriolar sclerosis, the latter commensurate with similar arteriolar changes in the other organs. We did not attempt to study serial sections of the entire bundle region. Permission was not granted to examine the brain.

DISCUSSION

Since high ventricular tachycardia and ventricular fibrillation are clinically indistinguishable from cardiac standstill, the electrocardio-

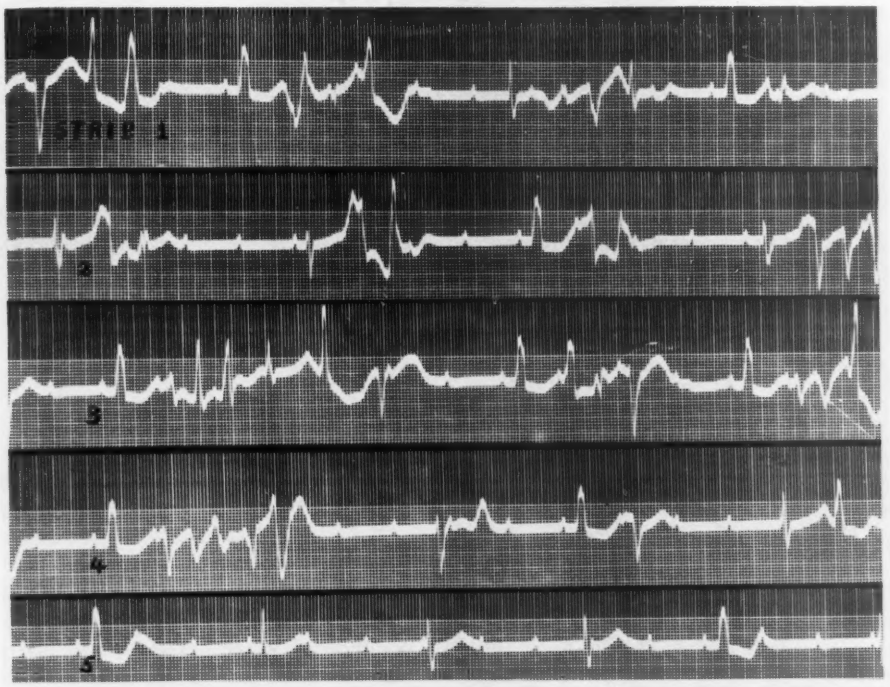

FIG. 2. Consecutive recordings of standard Lead II again demonstrating almost complete heart block and also chaotic heart action. There is a sinus rhythm, rate 92, as demonstrated by the regular appearance of P waves. The second beat in strip 5 is probably normally conducted. Beats such as the fourth in strip 1 and the first in strip 3 are interpreted as conducted with intermittent intraventricular block. Otherwise most of the beats are idioventricular and multifocal. In strip 4 there is a short burst of ventricular fibrillation. Again during this period the patient felt well and was not aware of a cardiac disorder. (A portion of this record has been reproduced in Katz, L.: Electrocardiography, ed. 2, Philadelphia, Lea & Febiger, 1946, p. 713.)

gram recorded during the Stokes-Adams seizure is the sole means of determining the exact disturbance in the cardiac mechanism responsible for the seizure. Schwartz[2] has studied extensively the problem of transient ventricular fibrillation, and offers evidence that a careful clinical study of the patient may aid in differentiating between syncope due to sudden ventricular asystole or an excessively slow and irregular idioventricular pacemaker on the one hand, and paroxysmal ventricular action on the other. To know whether the syncopal attack is due to cardiac standstill or to a high ventricular tachycardia or fibrillation is obviously important from a therapeutic standpoint.

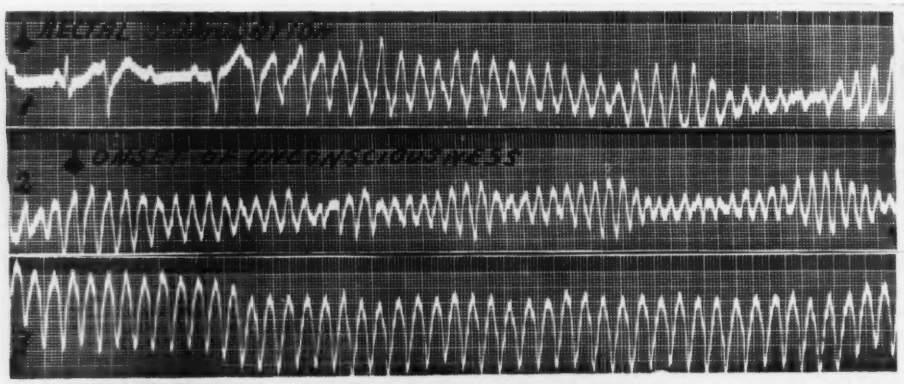

FIG. 3. Continuation of record shown in figure 2, standard limb Lead II. Two and two-tenths seconds following rectal dilatation there appears a multiform mechanism interpreted as ventricular tachycardia or coarse fibrillation. The characteristic sequence of events followed (see text) and within 9.2 seconds the patient became totally unconscious. Strips 1 and 2 are consecutively recorded; strip 3 was recorded later in the attack and represents ventricular tachycardia with a ventricular rate at times slightly over 300. Fifteen seconds following the last beat shown in strip 3 the attack ceased and there was a return of chaotic heart action interspersed with periods of almost complete block and near regularity (as in fig. 1). Consciousness returned within 2 or 3 seconds following cessation of fibrillation-tachycardia. Although P waves cannot be seen, regularly spaced a waves were noted in the jugular vein, indicating continuation of sinus discharge. This entire attack lasted 57.8 seconds and was reproduced repeatedly by the same maneuver. (A portion of this record has been reproduced in Katz, L.: Electrocardiography, ed. 2, Philadelphia, Lea & Febiger, 1946, p. 713).

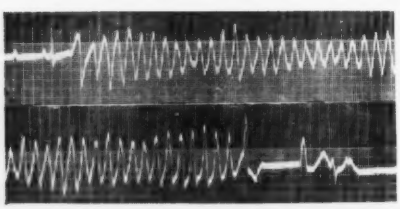

FIG. 4. Onset and offset of spontaneous episode of paroxysmal rapid ventricular action, continuous recording, standard limb Lead II. Total duration 11.8 seconds, patient becoming briefly unconscious towards the end. The patient's subjective complaints of faintness and apprehension just prior to loss of consciousness were correlated with the first few seconds of rapid ventricular activity and clinical asystole.

The frequent attacks of syncope caused by straining at stool and the constant induction of attacks by gentle digital stimulation of the rectum force one to consider the possible nervous path by which impulses from the rectum may reach the heart. It was suggested to us by Professor Albert Kuntz[3] of St. Louis University that through an intersegmental visceroviscera reflex, the stimulation from distention of rectal or pararectal sympathetic endings might transmit impulses into the spinal cord, and via the cardiac accelerator nerves increase sufficiently the irritability of a ventricular focus as to

cause a paroxysm of rapid ventricular action as was observed in our patient during a Stokes-Adams seizure.

Our survey of the literature has not disclosed a similar case. Wilson[4] mentions an instance of a 31 year old white man subject to numerous episodes of rapid ventricular action and syncope precipitated by exertion. He suffered one episode while straining on the bedpan, but a tracing was not made at this time. Schwartz[5] refers to a patient subject to seizures of "transient ventricular fibrillation following the type of exertion associated with straining at stool or when walking rapidly up an incline". The attacks in our patient however were uniformly induced by simple insertion of the gloved finger into the rectum.

Summary

A case of auriculoventricular block with Stokes-Adams attacks is presented. Electrocardiograms taken during attacks showed high ventricular tachycardia and fibrillation. The case is unique in that syncopal attacks were often caused by straining at stool and unfailingly induced by gentle digital stimulation.

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The Ventricular Electrokymogram

By L. C. Akman, M.D., A. J. Miller, M.D., E. N. Silber, M.D., J. A. Schack, M.D., and L. N. Katz, M.D.

Over 200 left ventricular electrokymographic tracings were obtained in 32 normal adults, averaging more than six sites explored per individual. Records were analyzed with respect to the relationship of certain designated points to simultaneously recorded heart sounds. Considerable variability was demonstrated in these relationships both in tracings from different ventricular sites in the same individual and between comparable tracings from different individuals. The meaning of the ventricular electrokymogram and its clinical applicability are discussed in the light of these findings.

SINCE THE development of the electrokymograph by Henny and Boone,[1] many articles have appeared in the literature concerning its utilization in the study of cardiac dynamics. The resemblance between the ventricular volume curve, as obtained in the dog, and the electrokymogram has been repeatedly stressed, and the various points of the electrokymogram have been given meaning by analogy to the volume curve and on the basis of some investigations with roentgenkymography.[2] However, conflicting viewpoints concerning certain phase relationships of the electrokymogram remain. These controversies, and the meanings that have been given by some to the electrokymogram, are such as to warrant further evaluation of their significance.

It is evident that significant advances in the use of the electrokymograph can be made only after complete clarification of the range of variability in tracings obtained from normal hearts. The present study concerns itself with a detailed analysis of left ventricular tracings obtained in 32 healthy young adults. A few tracings from the right ventricle in 5 normal subjects are included. Certain tracings obtained from abnormal hearts are presented in so far as they are pertinent to this analysis.

Method

The electrokymograph is a device by which graphic registrations of the movements of the heart and great vessel borders may be obtained. It consists essentially of a pick-up unit, which is mounted on a fluoroscopic screen, and a recording galvanometer. The pick-up unit contains a highly sensitive phototube and a narrow strip of fluorescent screen. The phototube converts light energy from the excited strip of fluorescent screen into electrical energy, the current thus produced being recorded by the galvanometer of an electrocardiograph. The excitation of the pick-up device is proportional to the amount of roentgen-ray transmission, the latter depending on the area, thickness and density of the tissue interposed between the x-ray tube and the slit of the pick-up. Connections are so arranged that an increase in x-ray transmission to the pick-up device causes a downward movement of the galvanometer string, and a decrease in x-ray transmission causes an upward movement of the string. Detailed descriptions of the electrokymograph are to be found elsewhere.[1, 3]

The equipment used in this study consisted of a Sanborn Electrokymograph with a modified mounting of the pick-up unit previously reported from this laboratory.[4] The Sanborn Stethocardiette was used for recording the heart sounds, which were used for time reference. Tracings were taken in midinspiration with the subjects in the upright position. The pick-up slit was placed perpendicular to the heart border so that one-third to one-half of its length fell within the cardiac shadow. The left ventricular border was explored in the posteroanterior and left anterior oblique positions. An apical tracing was obtained in the posteroanterior position and, in addition, three to four other tracings at equally spaced distances between the apex and the point of opposite pulsations. At least two other tracings were obtained from different sites on the posterior border of the heart with the patient in the left anterior oblique position. Thus, the left ventricle was explored by tracings taken from at least six different sites. The apical tracing, however, was not used for comparative measurements in this study. The heart sound pick-up device was placed in the left midaxillary line whenever possible. At no time was its position altered after satisfactory

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placement while the several electrokymograms were recorded, though adjustments in its contact with the skin were sometimes necessary.

All tracings obtained were analyzed with regard to the relation of comparable points on different tracings from the same individual to fixed points on the heart sound recordings. In order to avoid existing disagreements as to the meaning of certain points on the electrokymogram, all measurable phases were labeled alphabetically. Five landmarks on the electrokymogram were chosen for measurements because of their frequency of occurrence and relative ease of identification. Figure 1 shows the five designated points in an idealized electrokymogram. During the course of this investigation it was found that in certain curves points *A* and *B* were not discernible. When this occurred, measurements were made from the middle of the upward arc preceding the major downward deflection of the electrokymogram. This point is designated as *A-B*

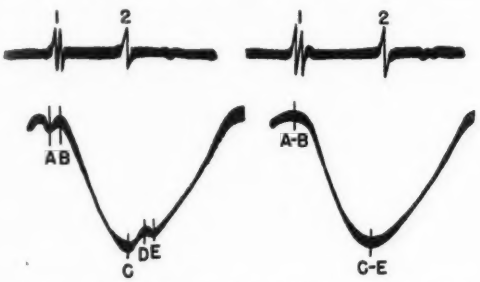

FIG. 1. Diagram on left indicates the 5 points chosen as landmarks in an idealized electrokymogram. The diagram on right indicates point references for curves in which the individual phases could not be identified. Explained in text.

(fig. 1). Whenever the characteristic W shape of the trough of the electrokymogram was absent, measurements were made from the point of change in direction from a downstroke to an upstroke. This point is shown in figure 1 as *C-E*.

Measurements consisted primarily of relating in time points *A* and *B* to the first major deflection of the first heart sound and points *C*, *D*, and *E* to the first major deflection of the second heart sound. Comparisons were then made of the intervals measured in tracings taken from different points on the left ventricular borders of each individual.

RESULTS

A. *Measurements*

Over two hundred left ventricular tracings were obtained in the 32 young healthy adults, averaging more than six left ventricular sites explored in each individual. Tables 1 and 2 indicate the pertinent measurements that were made, and the range of variation in these measurements from one tracing to another in the same individuals.

A breakdown of the *C* to *D* and *C* to *E* intervals illustrates the range of variation noted in measuring the various phases of the electrokymogram. The duration of the period of "isometric relaxation" was measured according to the criteria of Luisada, Romano and Torre,[5] that is, the time interval between points *C* and *D*. Ninety-three tracings taken in the postero-anterior position gave measurable endpoints. The *C* to *D* interval was found to vary between 0.02 to 0.14 second. The *C* to *E* interval, which is considered to be the isometric relaxation phase by Boone and associates,[6] varied between 0.08 and 0.23 second. Thirty-one tracings showed *C* to *D* intervals of 0.10 second or more, 57 were between 0.05 and 0.09 second, and 5 measured 0.04 second or less.

In 30 cases the *C* to *D* interval could be measured at more than one site. The difference in the duration of this phase between sites in the same heart was as much as 0.05 second. Twenty-two cases showed a variation of the *C* to *D* interval between sites of 0.03 second or less, and 8 cases showed a variation of 0.04 second or more. Points *C* and *D* did not always vary in the same direction, that is, a shift of point *C* or *D* to make the *C* to *D* interval longer was not necessarily counterbalanced by a shift of the other point in the same direction.

Multiple right ventricular sites were explored in the right anterior oblique position in five cases. The maximum differences in the duration of the *C* to *D* interval from various sites in the same cases were 0.05, 0.04, 0.03, 0.02 and 0.00 second, respectively.

B. *Contour*

Our studies indicate that contour variations in ventricular electrokymograms from normal adults are numerous. Nevertheless, there is a basic resemblance between tracings and a similarity in appearance of tracings taken from the same ventricular border.

Approximately half of the cases studied showed a rather characteristic left ventricular pattern in the left anterior oblique position. These, when present, were most marked at sites on the upper half of the visible border, and

were manifest in varying degree at sites on the lower half. The contour of these tracings tended to be smoothed-out and symmetrical. Usually, at approximately the beginning of the first heart sound, the curve showed a steep ascent. The descending limb after this ascent tended to mirror the ascending wave in its early portion, so that a smooth, relatively symmetrical, upward convexity was formed. The descending limb continued with little interruption to end usually 0.12 to 0.16 second beyond the first major deflection of the second heart sound. Figure 2 illustrates the prominent convexity just described. It is seen to occur during the early systolic phase of the cardiac cycle.

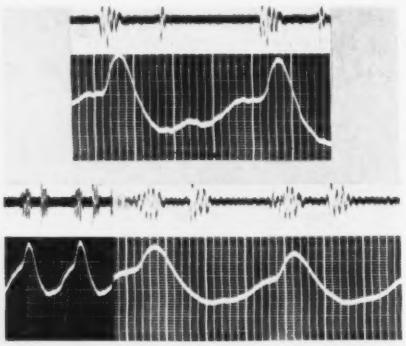

FIG. 2. Tracings obtained in 2 normal individuals from the upper third of the left ventricle in the left anterior oblique position. In each record, in this and subsequent figures, heart sounds are above and electrokymogram below. Time lines are 0.04 second apart. Ordinates show lines 1 mm. apart.

The contours of tracings obtained in the posteroanterior were more variable than those in the left anterior oblique position. Figure 3 illustrates a type of contour variation frequently found on exploration of the left ventricle in the posteroanterior position. It is seen that the single early systolic upward convexity in the lower tracing splits into two as tracings are taken from successively higher points on the ventricular border, until points *A* and *B* become discrete in the upper tracing. Figure 4 demonstrates variations in contour of the early systolic phase of the normal electrokymogram which simulate abnormal contrapulsatile movements in some tracings. Other examples of contrapulsatile movements in early systole in normal electrokymograms are shown in figures 2 and 3.

Figures 2, 3, 4, 6, 7 and 8 illustrate some of the normal contour variations that may be seen in diastole. Most commonly, the end of the systolic downstroke combines with the succeeding inscriptions to form a W-shaped trough; however, a V shape is not uncommon. In 19 individuals, one or more curves obtained in the posteroanterior position manifested a V-shaped, rather than the more characteristic W-shaped trough (figs. 5, 6). One case showed such a contour in all three of the left ventricular tracings obtained above the apex, two of which

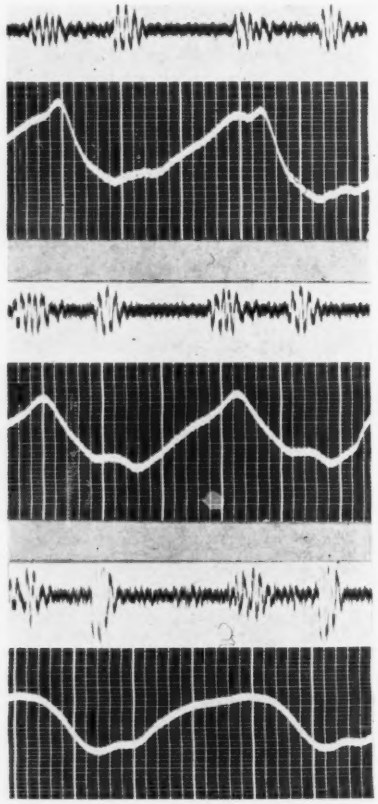

FIG. 3. Tracings illustrate splitting of the *A-B* segment into distinctly identifiable points *A* and *B* as recordings are made from successively higher points on the left ventricle in the posteroanterior position. The tracings are, from below upward, from the lower, middle and upper left ventricle respectively.

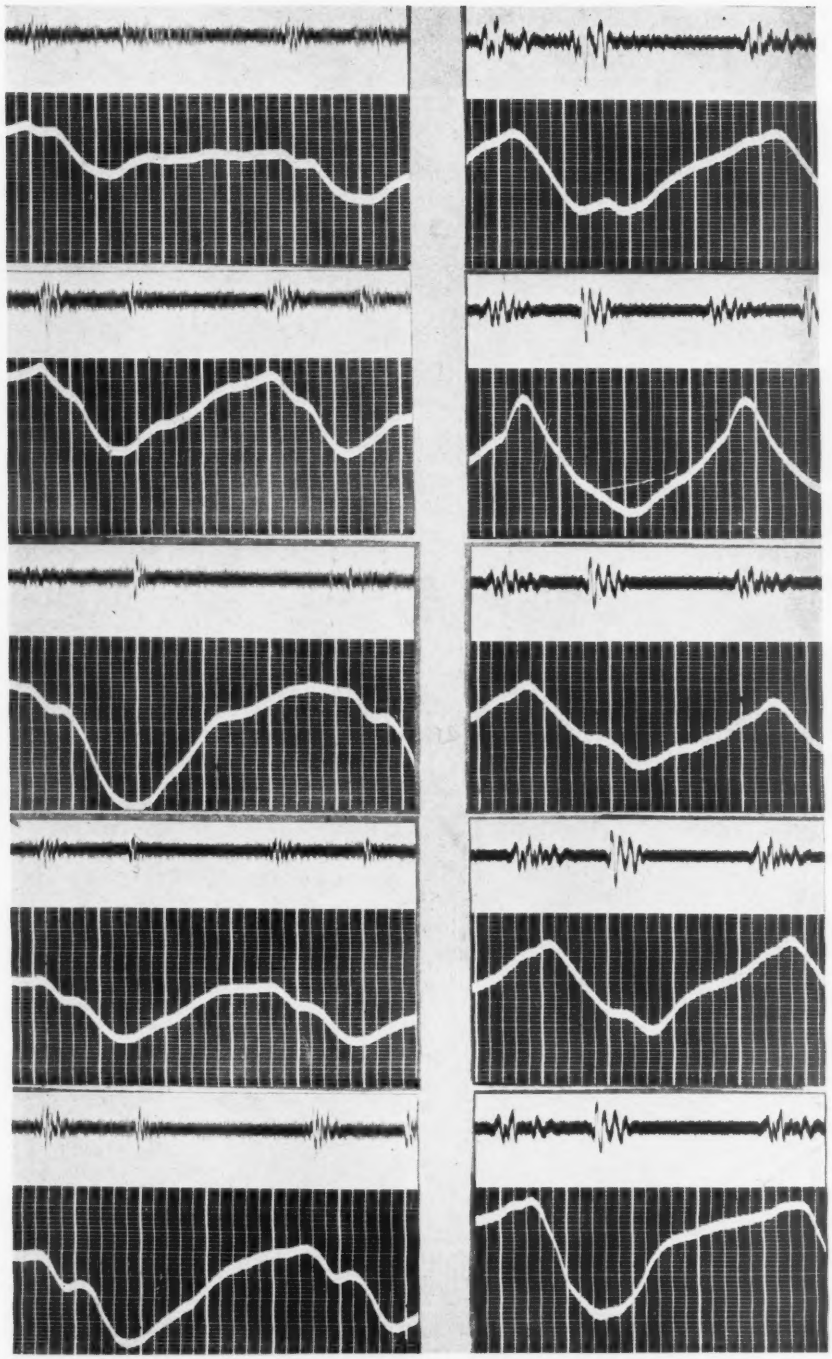

FIG. 4. Tracings from 2 normal individuals illustrating the range of contour variation found on exploration of the left ventricle in the posterior-anterior position. From below upward the tracings are taken: 1 cm. above apex, from lower, from middle, from upper, and from high up on left ventricle.

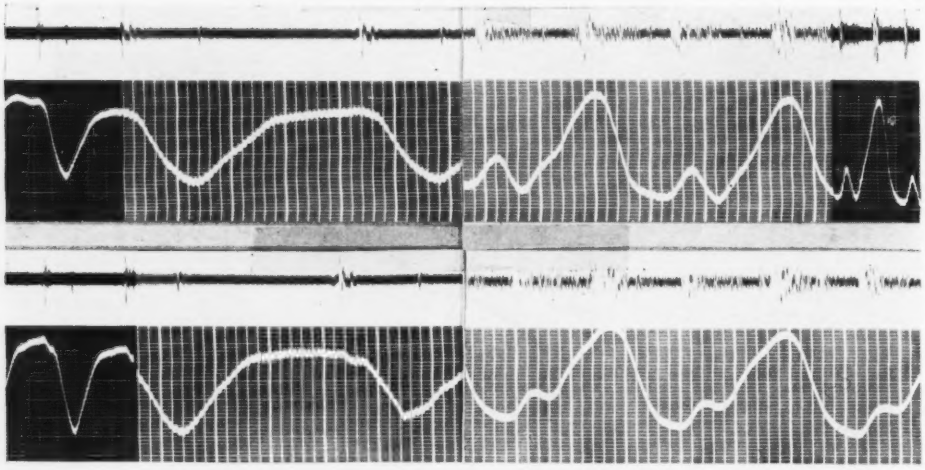

FIG. 5. Tracings on left illustrate a contour variation found in a normal individual in the posteroanterior position. Tracings on right are from an individual with aortic insufficiency. The lower curves are from the lower left ventricle; the upper curves are from the middle left ventricle. Note the absence of points *C*, *D* and *E* in the normal case, and their presence in the case with dynamic aortic insufficiency.

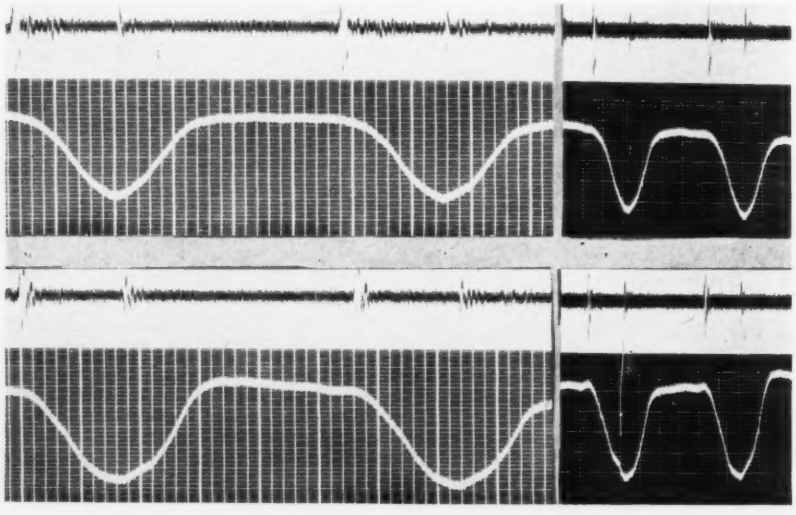

FIG. 6. Tracings demonstrate marked plateau during diastole in a normal individual, posteroanterior position. Upper curve: upper left ventricle. Lower curve: 1 cm. above apex. The curves at right were taken at a slower camera speed.

are shown in figure 5. Eight cases demonstrated the same V contour at both sites explored in the left anterior oblique position.

The *D* to *E* interval was generally manifest on the major ascending limb of the left ventricular electrokymogram. In some instances it became flattened or smoothed out, so as to become almost absorbed into that phase which has been designated the rapid inflow of diastole. Generally, in the posteroanterior position, the

middle of the W (point *D*) tended to occur at about the first part of the second heart sound; on the other hand, in the left anterior oblique position, point *D* (or *C-E*) often occurred well after the beginning of the second sound.

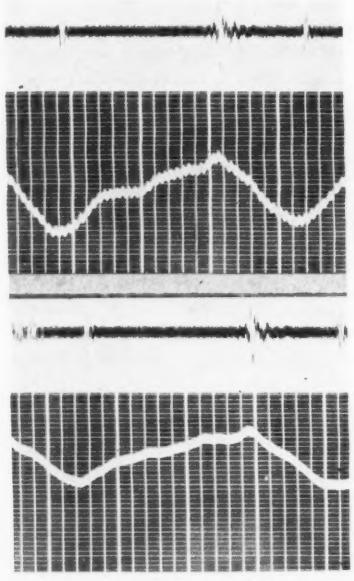

FIG. 7. Tracings showing contour variations in normal individual in posteroanterior position. Lower curve: lower left ventricle. Upper curve: middle left ventricle.

viduals (fig. 8). Though this phenomenon may have been initiated by a premature beat, the latter was not observed during the period of recording. The contour of alternate beats is seen to be considerably different.

DISCUSSION

Variations in the contour and time sequence of events in the normal electrokymogram are considerable. It would appear that interpretation of the electrokymogram on the basis of the volume curve may be misleading. Wiggers and Katz[7] have stressed the variability of contour obtained in volume curves from dog hearts by the cardiometric method. Moreover, they have stressed that the periods immediately preceding the onset of ventricular ejection and rapid filling are particularly susceptible to artefacts and that interpretations of phenomena seen in these phases of the cardiac cycle must be made with caution. In spite of these admonitions, the electrokymogram has been given meaning, often unjustified, on the basis of analogy to the idealized volume curve. Within certain limits, and subject to further experimentation, this analogy is allowable. However, it must be clearly understood that the volume curve of the textbook is a synthesis of many real curves. Movements of the dog heart into and out of the cardiometer tend to cause artefacts within the

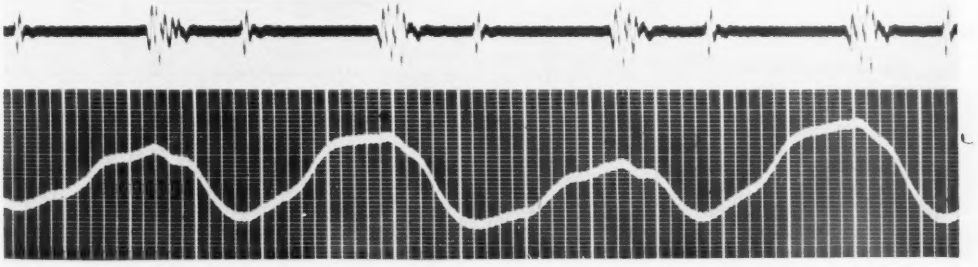

FIG. 8. Tracings showing mechanical alternans in a normal individual. Tracing obtained from the lower left ventricle in the posteroanterior position. Note the slight alteration in the first heart sound from one beat to the next.

Some of the tracings obtained were exceptionally smooth in contour, and symmetrical. In our series, such tracings appeared more apt to occur with slow heart rates (fig. 6). Mechanical alternans was noted in two normal individuals (fig. 8). Though this phenomenon may have been initiated by a premature beat, the latter was not observed during the period of recording. The contour of alternate beats is seen to be considerably different.

phases mentioned above. There is no reason to assume that movements of the human heart do not cause similar variations in contour in the electrokymogram.

The measurements obtained in this study

indicate that there is no consistent moment-to-moment time relationship between electrokymograms obtained at various sites on the left ventricular border and the heart sounds. Presumably this inconsistency could also be present in relation to other methods of timing, such as arterial or venous pulses. In at least 29 per cent of all cases in which comparative measurements could be made, the maximum variation in the timing of particular points on the electrokymogram from different sites in the same individuals was 0.04 second or more (table 1). A consideration of the magnitude of some of

TABLE 1.—*Variations in Time Relations of Points Under Consideration to the Heart Sounds (Postero-anterior Position).*

Reference point	Relation to 1st major deflection of 1st heart sound to point		Relation to 1st major deflection of 2nd heart sound to point		
	A	B		D	E
Number of cases in which measurements could be made at multiple sites on the left ventricle.	32	29	30	24	27
Number of cases showing maximum time variation between sites of 0.00 to 0.02 second.	15	13	16	13	9
Number of cases showing maximum time variation between sites of 0.04 to 0.06 second.	11	9	11	7	9
Number of cases showing maximum time variation between sites of 0.06 second or more.	2	2	3	3	5

the phases which have been measured by electrokymography[5, 6] accentuates the percentage error possible in this method.

Though different workers have used the volume curve and certain studies in roentgenkymography to analyze the electrokymogram, there is no complete agreement on the significance of all points. Boone and his co-workers[2] have designated point *A* (fig. 1) as the beginning of ventricular ejection. This interpretation seems reasonable in many of the tracings we have obtained. However, not infrequently, this point has been seen to be synchronous with the beginning of the first heart sound, and, in one case, this point occurred before the first heart sound (fig. 7). It is questionable, therefore, that point *A* consistently represents the beginning of the ejection period, since it is unreasonable to have an absent isometric contraction period in a normal heart.

The meaning of points *C*, *D* and *E* is also the basis of some controversy. In one of their earlier papers, Boone and associates[2] designated point *D* as synchronous with closure of the aortic valve. However, in their paper on the isometric relaxation phase[6] Boone and his co-workers used point *C* as the closure of the

TABLE 2.—*Variations in Time Relations of Points Under Consideration to the Heart Sounds (Left Anterior Oblique Position).*

Reference Point	Relation to 1st major deflection of 1st heart sound to point		Relation to 1st major deflection of 2nd heart sound to point			
	A	B	C	D	E	C-E
Number of cases in measurements could be made at multiple sites on the left ventricle	16	20	3	5	—	9
Number of cases showing maximum time variation of 0.02 second or less	10	12	1	3	—	4
Number of cases showing maximum time variation of 0.04 second or more	5	3	2	1	—	3

aortic valve. They measured isometric relaxation from point *C* to point *E*. Luisada[5] differs with Boone and associates[6] in that he maintains the opening of the mitral valve to be approximately synchronous with point *D*. Both groups of workers apparently now agree that point *C* is the beginning of isometric relaxation. However, in our experience, there may be a considerable time difference between the beginning of the second sound and point *C*. It is readily seen that a difference between these two landmarks of 0.04 second would cause a gross error in measurement of the isometric relaxation phase.

We have repeatedly noted that whereas one tracing taken from a particular site on the left

ventricle may clearly show points *C*, *D*, and *E*, another site may only show a V-shaped contour which we have labeled *C-E* (figs. 1, 5). It is unreasonable to assume that a particular part of the ventricular musculature manifests no protodiastolic and isometric relaxation phases while another part of the muscle does undergo these phases. Phillips[8] has stated that the V shape described is due to absence of the isometric relaxation phase, and has correlated this contour with aortic insufficiency. It is impossible to reconcile these two phenomena in the light of our experience. It is apparent that, though the V-shaped contour may be seen in aortic insufficiency, it also occurs in perfectly normal hearts (figs. 5, 6). Moreover, some studies which we have made of patients with dynamic aortic insufficiency have failed to demonstrate the immediate upstroke after the ventricular ejection phase; instead, the tracings have shown points *C*, *D*, and *E*. Such a tracing is depicted in figure 5. It is from a 19 year old boy with rheumatic aortic insufficiency who had a systolic blood pressure of 140 mm. Hg, and an undetermined diastolic pressure since sounds were present to 0.

Boone, Randak, Ellinger and Oppenheimer have presented evidence for their interpretation of points *C*, *D* and *E* by correlating simultaneous recordings of the auricular electrokymogram, the carotid pulse and the heart sounds.[6] Luisada and Fleischner[9] correlated the right ventricular electrokymogram, the right ventricular pressure, and the heart sounds in the dog. The present series failed to demonstrate a consistent relationship between points *C*, *D* and *E* and the heart sounds in tracings from the same individual. Presumably a similar variation could be expected with the carotid pulse and the auricular electrokymogram. Our evidence fails to indicate either that the points in question are directly related to valve action, or that the tracing reflects the volume curve closely enough to be more than roughly approximate. It is generally agreed that the contour changes associated with points *C*, *D* and *E* are due to positional changes of the heart. It may be that these points are, at least in part, due to the changes in cardiac position produced by the diastolic rebound of blood in the aorta. The coincidence of certain valve actions and changes in the graphic recording is most likely due to positional changes occurring in approximation to the valvular phenomena, and not to the valvular phenomena per se.

Illustrative electrokymograms have been chosen to demonstrate certain contours seen on exploration of the left ventricular borders. Additional tracings are shown to present examples of variations which we have found in normal individuals and which have been called abnormal by others. They have been aligned not only to show variations in normal cases, but also to demonstrate the variations in contour which occur from one site on the ventricular border to another.

The tracings in figure 4 (left column) reveal variations in the systolic slope due primarily to contour changes in relation to point *A*. In the high left ventricle tracing, the systolic phase following this point is such as to simulate a variant of decreased amplitude of contraction.[10] Many tracings we have obtained in normals are similar to illustrations and diagrams shown by Sussman and co-workers[11] and by Luisada and associates[10] as occurring after myocardial infarction. The latter authors make no differentiation, in their diagrams of abnormal tracings with myocardial infarction, between tracings taken in the posteroanterior position and tracings taken in the left anterior oblique position. Certain of the tracings classified as abnormal[10] are illustrated here as occurring in normal individuals. They are: (a) decreased amplitude of the ventricular wave (figs. 4 and 7); (b) early systolic distention (figs. 3 and 4); (c) late onset of ventricular systole (fig. 4); (d) presystolic distention (fig. 4); (e) early diastolic rebound (figs. 3, 4 and 7). Figure 4 (right column) illustrates, in a normal case, a contour indicated by Sussman and associates[11] as abnormal. We have also noted that the left anterior oblique tracing in the second case reported by these workers is not unexpected as a tracing from that border.

Although many of the tracings reported by Luisada and co-workers[10] in myocardial infarction are undoubtedly abnormal, a number fall well within the range of normal as seen in our study. The factor of standardization must be

considered when dealing with suspected abnormalities due to decreased amplitude of contraction. A few of our tracings (figs. 5, 6) are of the type considered by Gillick and associates[12] to be indicative of constrictive pericarditis. Again, although this type of curve may be seen in constrictive pericarditis, it is also seen in the normal. It would appear that the demonstration of this contour is more frequent in the presence of slow ventricular rates.

The differences in contour found in tracings from different sites on the left ventricular surface indicate the need for a more careful consideration of just how closely the electrokymogram reflects the volume curve and how much it reflects only positional movements of either the whole or parts of the heart. Though it is generally agreed that the electrokymogram is not a volume curve, the resemblance between the two makes their identification extremely tempting. A combination of many factors determines the character of the tracing obtained from any particular site on the ventricular border, and the effects of certain of these factors are opposite to each other and to that of the total ventricular volume change. The influences of rotational and positional change have been noted repeatedly.[2, 6, 13, 14] The latter, as mentioned above, we believe to be of primary importance in producing points *C*, *D* and *E*. In addition, consideration must be given to changes in configuration of the heart during the early systolic phase in producing the points found so often in the electrokymogram. Roentgenographic studies have demonstrated the preponderant shortening of the long axis of the heart during contraction so that it tends to assume a globular shape and increase its anteroposterior diameter. It is well known that the base of the heart moves toward the apex. This has been repeatedly demonstrated in this laboratory and elsewhere. Hamilton and Rompf,[15] observing fluoroscopically the movements of metal markers implanted in the dog heart, and Wolferth and Margolies,[16] studying the movements of cardiac calcifications in the human heart by means of roentgenkymography, have shown the important feature of left ventricular contraction to be shortening of the long axis. Both papers note the great part played by movement of the A-V septum, not visible normally by fluoroscopy, in decreasing ventricular size during contraction. Wolferth and Margolies also observe that, because of the preponderant shortening of the longitudinal axis of the heart, the left border may actually move outward during early systole. Roesler[17] reported, on the basis of roentgenkymography studies after lipiodol instillation into the pericardial sacs of rabbits, a movement of the atrioventricular groove of one third to one fourth the total length of the heart while the border and apex moved but little. These studies would indicate that, with a stationary slit as used in electrokymography, the tracing does not depict the movement of any one point on the heart, but rather reflects the movements of the heart that occur under the slit.

The relation of various points on the electrokymogram to the phases of the heart cycle is variable. It is concluded that great caution should be used in the judgment of contour changes in the electrokymogram before considering them abnormal.

Summary

1. Left ventricular electrokymograms from normal individuals have been analyzed with respect to the relationship of certain designated points to simultaneously recorded heart sounds.

2. Considerable variability has been shown to exist in these relationships, both between comparable tracings from different individuals and in tracings obtained from different sites on the ventricular border in the same individuals.

3. The implications of these findings are discussed with reference to the meaning of the left ventricular electrokymogram.

4. It is concluded that certain electrokymographic contours previously considered abnormal can be found in tracings from normal hearts. Caution must therefore be used in the interpretation of electrokymograms both as to contour and their depiction of the phases of the heart cycle.

Acknowledgments

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Correlation of Simultaneously Recorded Electrokymograms and Pressure Pulses of Human Heart and Great Vessels

A Preliminary Report

By A. H. Salans, M.D., J. A. Schack, M.D., and L. N. Katz, M.D.

In order to define more precisely meaningful points on ventricular and great vessel electrokymograms, intraluminal and intracavitary pressures have been simultaneously recorded. Electrokymograms of the superior vena cava and the pulmonary artery show remarkable constancy of time relationships with simultaneously recorded intraluminal pressure curves. The ventricular electrokymogram is more difficult to define and its limitations are discussed.

FOLLOWING the development of the electrokymograph by Henny and Boone,[1] great interest in the use of this instrument as a tool in clinical investigation has been aroused. The application of this instrument to the study of many types of cardiac lesions has been reported.[2–5]

During the past 18 months more than 100 normal and abnormal subjects have been studied with this instrument in our laboratory, utilizing the recorded heart sounds, the carotid sphygmogram or the electrocardiogram as the primary points of time reference. We have been impressed with the inconstancy in the timing of the electrokymographic events obtained in ventricular tracings when studied with any of the above methods. The objections to each of these timing devices are well known. Thus, the factors of variability in the carotid sphygmogram which may be consequent upon variation of the rate of blood flow, elasticity and distensibility of the vessel have been discussed.[6] The validity of a comparison of the mechanical events in the cardiac cycle with the electrocardiogram has been called into question.[7] The heart sounds represent a fusion of noises arising from both ventricles and are thereby limited as a timing device for events occurring separately in each chamber.[8]

In an attempt to define more precisely the significance of the electrokymographic tracings obtained from the chambers of the heart and the great vessels in man we have undertaken a correlation of these tracings with the most direct measurements possible, the intraluminal and intracavitary pressure curves in man. Some data of this kind has been recently obtained in the dog.[9]

Materials and Methods

Concurrent right heart catheterization and electrokymography of the cardiac silhouette were performed in 6 patients. One patient was a child of 5 in whom the diagnosis of tetralogy of Fallot was made. Another was a 68 year old man with arteriosclerotic heart disease and chronic cor pulmonale. Four patients were children of 8 to 15 years of age who were subsequently found to be normal.

Right heart catheterization was performed according to the technic previously described.[10] The electrokymographic recordings were obtained with the patient in the recumbent position holding his breath in midinspiration.

Intraluminal and intracavitary pressures were recorded with a Sanborn electromanometer. The kymographic apparatus employed was essentially that developed by Henny and Boone[1] as modified by Luisada and co-workers[11] and Grossman and Tiger.[12] Simultaneous recordings of Lead II of the electrocardiogram, intraluminal and intracavitary pressures obtained via the right heart catheter, direct brachial arterial pressure and the electrokymogram were made with a four channel direct writing Sanborn Poly-Viso apparatus.

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The frequency response and sensitivity of the electrokymographic apparatus has been described elsewhere.[13] The galvanometer response to a square wave input (damping 71 per cent of critical) is 95 per cent complete in 0.01 second. The time lag of an impulse through the catheter at 37 C. was found to be 0.015 second.[14] Therefore the time lag in the pressure and in the electrokymographic systems are approximately of the same order.

While some of the pressure pulses show artefacts, these were not serious enough to disturb the measurements made. No claim is made, however, that the pressure pulses are precise measures without phase lag of events recorded. They are adequate, nonetheless, for the purposes in hand, we believe.

Results

Pulmonary Artery Electrokymograms

Timing. We have compared the electrokymographic tracing obtained from the pulmonary artery with the pulmonary arterial pressure curves with respect to the points of origin of the anacrotic limb and of the dicrotic notch and the interval between these two points which delineates the ejection phase of the right ventricle.

Electrokymograms have been obtained with the slit of the "pick-up" device positioned perpendicularly to the lowest point of the main pulmonary artery (border tracing) and to the terminal 4 cm. of the indwelling catheter. The patient was placed either in the posteroanterior or left posterior oblique position.

In 3 normal cases the beginning of rise of the anacrotic limb of the electrokymogram of the pulmonary artery border (point A_k) preceded the beginning of the rise of the anacrotic limb in the pulmonary arterial pressure curve (point A_p), by an average of 0.02 second with a range of from 0.00 to 0.03 second (fig. 1). The dicrotic notch of the pulmonary arterial border electrokymogram (point D_k) followed that of the pulmonary pressure (point D_p) by an average of 0.03 second with a range of 0.01 to 0.04 second. The duration of the ejection phase, i.e., point A to point D, averaged 0.28 second with a range of 0.27 to 0.31 second in the pulmonary pressure tracings in comparable beats. This extent of variation was noted in the pulmonary artery border electrokymograms.

When the slit of the "pick-up" device was placed completely within the visible shadow of the main pulmonary artery and parallel to the terminal 4 cm. of the indwelling catheter, densograms were recorded with the following results (fig. 2). Point A_k was found either to precede, coincide or follow point A_p, ranging from preceding by 0.03 second to following by 0.07 second. The dicrotic notch, point D_k, was found to follow point D_p by an average of 0.02 second, with a range of 0.01 to 0.03 second. The duration of the ejection phase of the right ventricle as reflected in the pulmonary artery densogram was found to average 0.31 second. Comparable beats of the pulmonary artery pressure curve demonstrated a ventricular ejection time of 0.28 second.

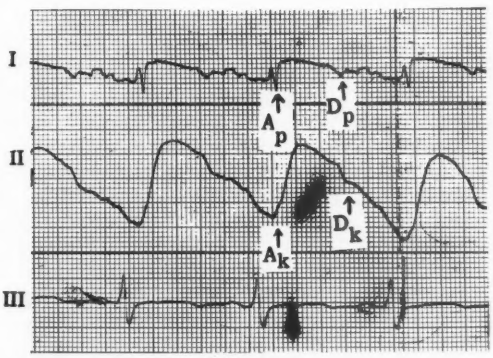

FIG. 1. Pulmonary arterial electrokymogram (border tracing). Recorded at 50 mm./sec. I. Pulmonary arterial pressure (distorted by artefacts). II. Pulmonary arterial electrokymogram. III. Electrocardiogram. Abscissae in mm. Ordinates in 0.04 second in this and subsequent figures. Discussed in text.

The time relationship of the curves under consideration to the onset of the QRS deflection of the Lead II electrocardiogram were as follows: The beginning of the rise of the anacrotic limb of the pulmonary pressure curve (point A_p) followed the onset of the initial deflection of the QRS by an average of 0.08 second (corrected for time lag of 0.015), with a range of 0.05 to 0.11 second. However, in each individual case the variation was only 0.02 second from beat to beat. The electrokymogram of the border movement revealed point A_k to follow the onset of QRS by an average of 0.07 second with the same order of variation observed in the pulmonary artery

pressure tracings. The electrokymogram of the pulmonary artery density revealed point A_k to fall off slowly. In most instances a discernible dicrotic notch is present.

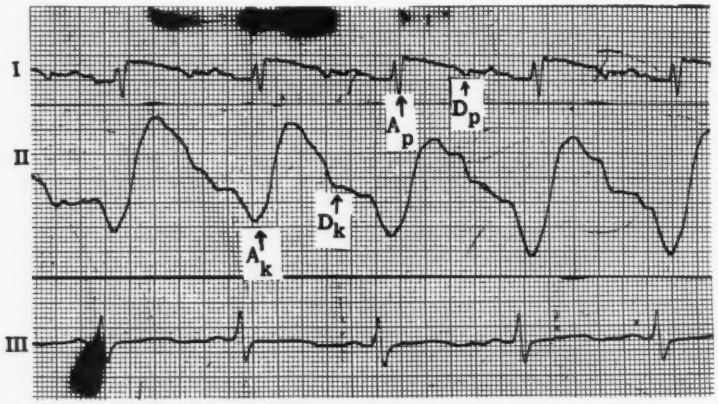

FIG. 2. Pulmonary arterial electrokymogram (densogram tracing). Recorded at 50 mm./sec. I. Pulmonary arterial pressure (distorted by artefacts). II. Pulmonary arterial electrokymogram. III. Electrocardiogram.

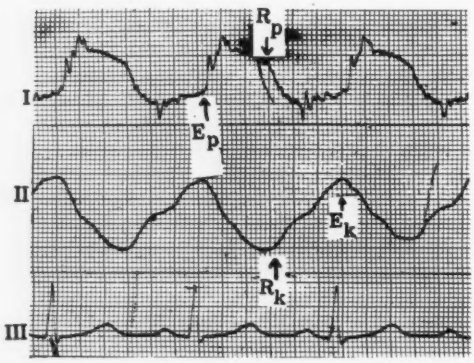

FIG. 3. Right ventricular electrokymogram (mid-border tracing). Recorded at 50 mm./sec. I. Right ventricular pressure (distorted by artefacts.) II. Right ventricular electrokymogram. III. Electrocardiogram. See text.

follow the onset of QRS by an average of 0.06 second with a variation of only 0.02 second within a single case (fig. 2).

Contour. The similarity of the contour of the electrokymograms obtained from the border movement of the pulmonary artery to the density changes within the pulmonary artery is apparent. In both instances well defined, steeply rising anacrotic limbs are present. These reach a rather rounded peak and then

Right Ventricular Electrokymograms

Timing. Following the withdrawal of the catheter into the right ventricle, the patients were rotated into the left posterior oblique position. Electrokymograms of the border movement of the right ventricle were then obtained in the region of the tip of the catheter (fig. 3). The beginning of the fall in the electrokymogram, which is considered by some to represent the beginning of ventricular ejection (point E_k), may precede, coincide or follow the rise in the ascending limb of the ventricular pressure curve (point E_p), varying from 0.03 before to 0.06 second after this event. Point R_k, marking the end of the fall in the ventricular electrokymogram, varied considerably when compared with the change in slope of the fall-off in the ventricular pressure curve (point R_p), sometimes preceding and sometimes following this point. This is in part due to the difficulty in determining the point R_k on the ventricular electrokymogram. However, it may also represent errors inherent in the measurement of the ventricular pressure curves. The difficulty in accurately defining the points on the ventricular electrokymograms obtained in this study prevents the comparison of ventricular ejection times as determined by the border

electrokymogram with those obtained from intracavitary pressure tracings. It is apparent that the declining limb of the ventricular electrokymogram represents more than the motion imparted to the heart border by ventricular emptying.

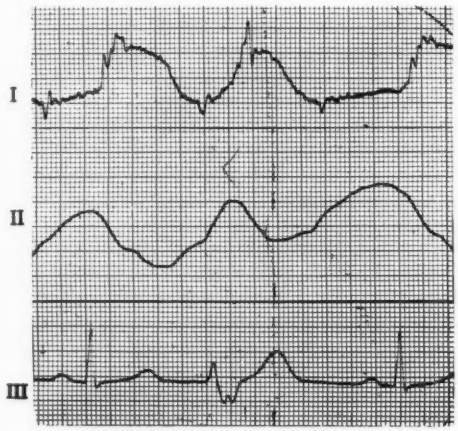

FIG. 4. Same as figure 3. See text.

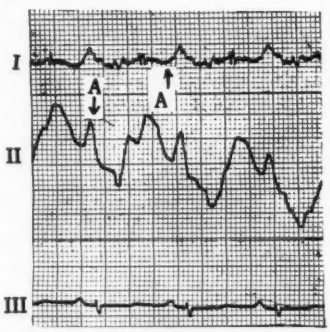

Fig. 5. Right auricular electrokymogram (border tracing). Recorded at 25 mm./sec. I. Right auricular pressure (distorted by artefacts). II. Right auricular electrokymogram. III. Electrocardiogram. See text.

Contour. The ventricular electrokymograms presented here consist essentially of a declining and an ascending limb. Variations in slope of either limb could be correlated to some degree with events known to occur in the volume curve of the dog heart. However, the accumulated data is insufficient for further elaboration at this time.

Of particular interest is the change in contour of the ventricular electrokymogram with the occurrence of a premature beat (fig. 4). It will be seen that this change is accompanied by a change in the intracavitary pressure curve. In this instance the border electrokymogram closely reflects the mechanical activity of the ventricle.

Electrokymograms of the Right Auricle and Large Veins

In two instances, electrokymograms of the border movements of the right auricle were recorded after the catheter had been withdrawn into this chamber (fig. 5). The beginning of the fall of the A wave of the auricular electrokymogram followed the beginning of the rise of A wave of the auricular pressure curves by 0.05 second. The A waves of both the auricular electrokymogram and the auricular pressure curve bore precise relationships to the end of the inscription of the P wave of the electrocardiogram. As will be noted the other points of the auricular electrokymogram tend to follow those of the auricular pressure curve.

Figure 6 presents an electrokymogram obtained as a density recording over the superior vena cava. In this instance the patient was in the posteroanterior position and the tip of the catheter had been withdrawn into this vessel and was lying approximately 2 cm. from the slit focus of the pick-up device. It will be noted that the electrokymogram obtained shows prominent A and C waves. These waves follow their counterparts in the superior vena caval pressure curve by 0.04–0.05 and 0.07–0.09 second respectively. The P-R interval of the electrocardiogram averaged 0.16 second at this time as did the A-C interval of the electrokymogram.

Correlation of Electrokymograms and Pressure Curves in the Presence of Intraventricular Conduction Defect

In the course of the catheterization of a 15 year old girl, a right bundle branch system block of the "S" type appeared and persisted throughout the procedure. The bundle branch block disappeared 45 minutes after comple-

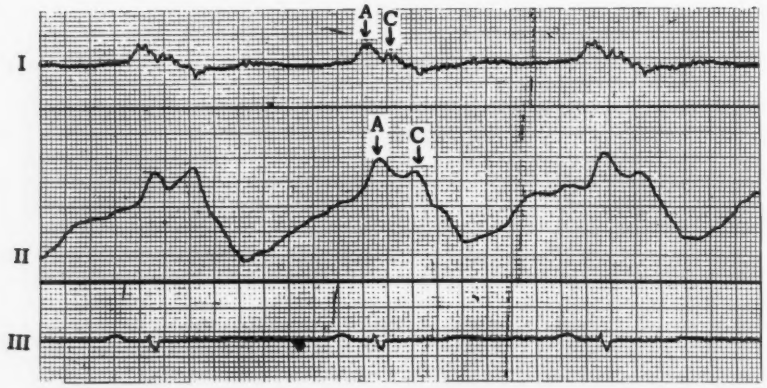

FIG. 6. Superior vena caval electrokymogram (densogram tracing). Recorded at 50 mm./sec. I. Superior vena caval pressure (distorted by artefacts). II. Superior vena caval electrokymogram. III. Electrocardiogram. See text.

tion of the catheterization. The patient was reexamined two weeks later and electrokymograms of the cardiac chambers and great vessels obtained. At this time no evidence of defective intraventricular conduction was present. There was no evidence of organic heart disease.

The electrokymograms of the aortic and pulmonary artery borders are presented in figures 7 and 8 both during and after the production of the right bundle branch system block. During the time of block the beginning of rise in the anacrotic limb of the pulmonary artery electrokymogram followed the nadir of the R wave by 0.11 second, and the beginning of the rise of the anacrotic limb of the electrokymo-

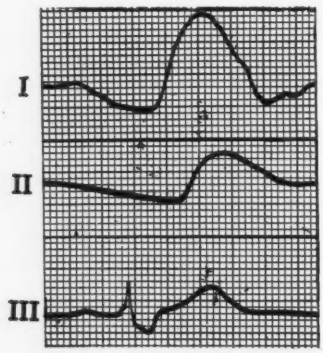

FIG. 7*A*. Aortic knob electrokymogram. Recorded at 50 mm./sec. during right bundle branch system block. I. Aortic knob electrokymogram. II. Brachial arterial pressure. III. Electrocardiogram. See text.

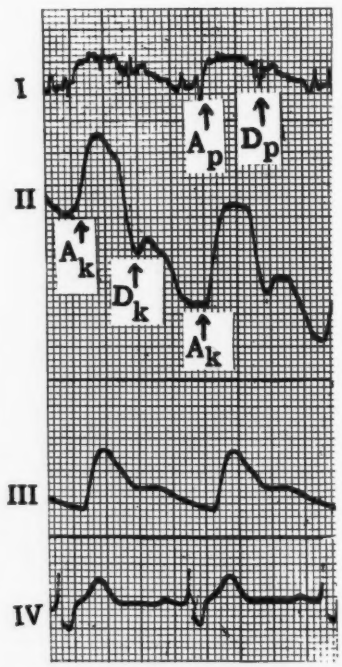

FIG. 7*B*. Pulmonary arterial electrokymogram (border tracing). Recorded at 25 mm./sec. during right bundle branch system block. I. Pulmonary arterial pressure. II. Pulmonary arterial electrokymogram. III. Brachial arterial pressure. IV. Electrocardiogram. Same patient as 7*A*.

gram obtained from border of the aortic knob followed the nadir of the R wave by 0.07 second. Following the disappearance of the block, the time relationship of the aortic electrokymogram and the electrocardiogram was unchanged. However, the beginning of the rise in the anacrotic limb of the pulmonary artery electrokymogram now occurred 0.07 second after the nadir of the R wave of the electrocardiogram. Thus, an average prolongation in the time of onset of filling in the pulmonary artery, as judged by these measurements, of 0.04 second existed during the period of right bundle branch system block.

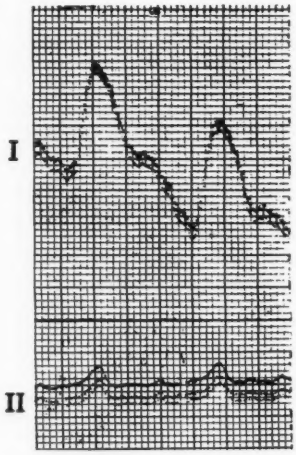

FIG. 8A. Aortic knob electrokymogram (border tracing). Recorded at 25 mm./sec. after the disappearance of right bundle branch system block. I. Aortic knob electrokymogram. II. Electrocardiogram. Both curves show artefacts. Same patient as 7A.

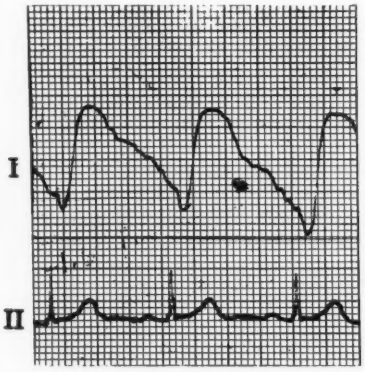

FIG. 8B. Pulmonary arterial electrokymogram (border tracing). Recorded at 25 mm./sec. after the disappearance of right bundle branch system block. I. Pulmonary arterial electrokymogram. II. Electrocardiogram. Same patient as 7A.

DISCUSSION

While the data presented in this report must be considered as preliminary, certain facts are clear from the material presented.

First, the electrokymographic deflections obtained from the superior vena cava and the pulmonary artery show a remarkable constancy of time relationship with simultaneous intraluminal pressure curves. The densograms obtained over these areas follow with a somewhat greater variation. The resemblance of the contours of both the border and density electrokymograms of these vessels to the intraluminal pressure pulses is evident. Thus, these electrokymograms may be said to reflect closely the mechanical activity of the heart as it is propagated to the adjacent major vessels. Distortions due to impacts of adjacent structures appear to play an insignificant role. However, elongation and pendulum motion of the great vessels occurring with the systolic descent of the base of heart may in part explain the earlier rise of the anacrotic limb of the pulmonary artery electrokymogram over comparable points in the pulmonary artery pressure curves.

The ventricular border electrokymogram is more difficult to define. The inability to establish closely meaningful points on these tracings as compared with those in the large vessels may be responsible for this difficulty. It is apparent that the declining limb of the ventricular electrokymogram represents more than the systolic emptying of the ventricle. However, the respective contribution of isometric contraction, rotation of the heart, isometric relaxation, and other factors cannot be evaluated at this time.

Further study of this problem is in progress. It is our opinion, however, that until more complete definition of the physiologic meaning of these tracings is obtained, clinical applications must be approached with great caution.

Summary

1. The correlation of electrokymographic tracings obtained from the pulmonary artery, right ventricle, right auricle and superior vena cava with simultaneously recorded intraluminal and intracavitary pressure curves is presented.

2. A case of transient right bundle branch system block produced during cardiac catheterization has been studied. Asynchronism of ventricular ejection during the period of block was demonstrated by means of electrokymography of the great vessels.

3. Electrokymographic deflections obtained from the pulmonary artery and superior vena cava show a remarkable constancy of time relationships with simultaneous intraluminal pressure curves. The densograms obtained over these areas follow with a somewhat greater variation.

4. Meaningfulpoints on the ventricular electrokymogram are difficult to define and until more precise definition of the physiologic meaning of these tracings is obtained, clinical applications must be approached with great caution.

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Aortography in Infants

By JOHN D. KEITH, M.D., AND CONSTANCE FORSYTH, M.D., M.R.C.P.

Making a diagnosis of a patency of a ductus arteriosus is often difficult in the first few months or first year of life. When the diagnosis is in doubt, one may profitably turn to angiocardiography for help. In this paper a method of demonstrating the patent ductus by the injection of contrast medium is described. The practical importance of the correct diagnosis is presented with reference to 4 cases treated surgically in the early months of life. Demonstration of coarctation of the aorta by this method is also discussed.

TO ANYONE interested in angiocardiography in infants, the studies of Barclay and his co-workers[1] on the fetal circulation are most stimulating. Their investigations of the circulatory changes at birth, in lambs, provide a most useful background in studying similar processes in man. The clarity of their methods, using contrast media to demonstrate the ductus arteriosus, makes one wish it were possible to investigate human subjects as thoroughly. Although this is not possible, much can be done to investigate infants in the first year of life, and especially in the new-born period, by similar methods.

Probably the chief value of the method to be described is in the study of patent ductus arteriosus, but one may also investigate coarctation of the aorta and other anomalies of the aortic arch by this method. Patency of the ductus arteriosus has been demonstrated in infants by clinical means and by examination. Sometimes the presence of a continuous murmur in the pulmonary area indicates this anomaly. Such a murmur has been noted in a few premature babies. However, there may be simply a systolic murmur and the presence of a patent ductus can only be suspected.

The necessity of early diagnosis has become more imperative now that surgical closure of the ductus can be performed with relative ease and safety. The problem was brought forcibly to our attention recently, when an infant of 2 months was admitted to hospital with cardiac failure. The presence of a patent ductus was suspected, and the diagnosis was confirmed by aortography. The baby was successfully operated upon at 3 months of age with subsequent cure of the heart failure.

As surgical technic improves, it may be possible to operate on coarctation of the aorta, and on other anomalies of the aortic arch, in infancy. With these observations in mind, it was decided to study suspected cases of patent ductus arteriosus and coarctation of the aorta in infants by angiocardiography and relate the results to the clinical findings.

METHOD

In 1942, Castellanos[2] referred to the injection of contrast media up the brachial artery into the aorta. We have adapted this method for our use in studying the aorta and vessels arising from it, in infants.

A short longitudinal incision is made in the skin above the antecubital space of the left arm, and the tissues dissected down until the brachial artery is exposed. It is then ligated distally, and a number 18 needle, or larger if possible, is inserted up into the artery. The baby is then placed in the left anterior oblique position on the angiocardiography table, beneath the x-ray tube. A syringe is prepared containing 3 to 6 cc. of 35 per cent Diodrast, the stylet is removed from the needle and the syringe is attached to it. A small amount of blood is allowed to flow out from the artery into the syringe to make sure the needle is patent, and that no air is present. The instrument for taking x-ray films is then started, and the injection is made in as short a time as possible. The developed serial x-ray films taken at the rate of about three or four a second show the contrast medium in the aorta and great vessels. This contrast medium clears very rapidly and has usually disappeared within two to three seconds.

The left arm is used almost invariably because the left subclavian artery arises directly from the aorta. When the right arm is used a large proportion of the

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contrast medium goes into the carotid artery and the cerebral vessels. If dye is injected into the left arm rapidly enough, a considerable amount of the contrast medium will reach the aorta proximal to the entrance of the subclavian artery, and may reveal the whole aortic arch to the aortic valve, as well as the descending aorta. An example of this technic is shown in figure 1 which illustrates a normal aorta.

Observations

Twenty-six aortograms have been made on infants and young children. Most of these infants were in the first few months of life, although 2 children were over 2 years of age. In studying the findings in these infants, there are two obvious groups: (1) those with a normal aortogram, and (2) those with evidence of

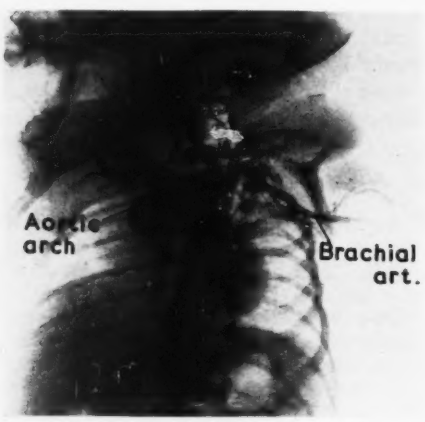

Fig. 1. Aortogram showing normal aorta

patent ductus arteriosus, persistent truncus, or coarctation of the aorta.

Group 1. In the first group there were 13 patients who had no evidence of any abnormality in the aortogram. Most of these were in the first few weeks or months of life. The average age was 3 months, apart from one child of 2½ years and one of 4 years. The youngest was 5 days old. These infants had a variety of conditions that led to the making of the aortogram. In 6 patients in group 1 the diagnoses made clinically or at necropsy were as follows: tricuspid valve opening into the left ventricle, atrioventricularis communis, pulmonary veins emptying into the right auricle, left coronary arising from the pulmonary artery, idiopathic dilatation of the pulmonary artery and tetralogy of Fallot. In 2 patients the diagnosis was ventricular septal defect. In 2 patients Lutembacher's syndrome was thought to be present. In 3 infants the hearts were considered to be normal.

Certain normal findings were common to all children in group 1. In all cases the brachial and left subclavian arteries were clearly visible. Many small branches arising from the subclavian artery were also clearly delineated. The vertebral artery stood out with clarity. The descending aorta could be seen from the point of entrance of the subclavian artery down into the lower abdomen. A short portion of the aortic arch beyond the entrance of the subclavian was visible in each case; the amount of the arch showing largely depended upon the rapidity with which the injection was made into the brachial artery. The left carotid artery did not show unless the contrast medium backed up into the aortic arch. In some cases the whole aortic arch was visible and then all the great vessels arising from it were seen. The left internal mammary artery was outlined in every case. The intercostal vessels were frequently visible but not invariably so. The superior and inferior mesenteric arteries could be seen but the hepatic arteries and renal arteries could not be identified with any certainty.

One case was a baby of 5 days who had a normal aortogram with the exception of a bulge at the site of the entrance of the ductus arteriosus into the aorta. There was no evidence of filling of the ductus or the pulmonary vessels with Diodrast. The bulge was therefore taken to be associated with the antenatal channel of blood through the open ductus. It was concluded that the ductus had closed some time in the five days preceding the aortogram. (See fig. 1.)

Group 2. In this group there were 14 cases. Their findings have been summarized in table 1. There were 8 cases of patent ductus arteriosus studied by aortography. One infant was added to the group because the clinical diagnosis was confirmed at operation, although no aortogram was done. There were 4 cases of

coarctation of the aorta, and one of persistent truncus arteriosus.

In the 8 infants in whom the ductus was delineated by the contrast medium, the ages varied from 10 days to 15 months, the average being 4 months. Two of these infants had cyanosis, and 6 had no evidence of cyanosis. Three had dyspnea and signs of early failure, and 5 had no dyspnea and no signs of failure. A thrill was palpable in one patient. This occurred in a 15 month old child and was palpable in the pulmonary area. In 2 instances the murmur was continuous, in 2 it was present in systole and extended into early diastole,

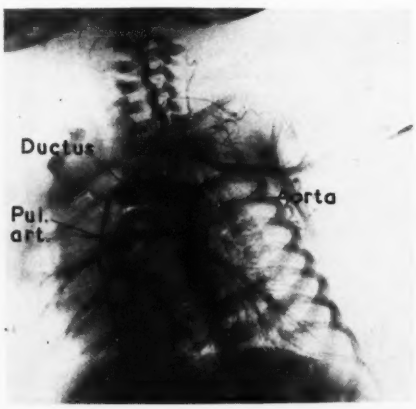

FIG. 2. F. H., age 3 weeks. Patent ductus arteriosus. Aortogram showing elongated ductus arteriosus filling from the aorta and outlining the pulmonary artery and its branches.

in 2 it was heard in systole only, and in 2 no murmur was heard. Under the fluoroscope 3 showed grossly enlarged hearts, 2 moderately enlarged hearts, and 3 showed slightly enlarged hearts.

The aortogram showed filling of the pulmonary artery from the aorta in all 8 infants, but in only one could the ductus itself be outlined as it filled with contrast medium from the aorta (fig 2). In this patient the ductus was abnormally long and the aorta and pulmonary arteries were distinctly separated. In the other cases the aorta and pulmonary artery were within a few millimeters of each other, and the shadow of the two vessels overlapped sufficiently to prevent the recording of a clear-cut image of the ductus. However, the filling of the pulmonary artery from the aorta at the usual site of the ductus permitted the diagnosis to be made (fig. 3). The diagnosis of a patent ductus arteriosus was confirmed definitely in 5 of the 8 infants; 2 died at a later date and at postmortem examination a patent ductus was readily demonstrated; in 3, the ductus was exposed at operation and successfully ligated.

The presence of other congenital defects of the heart was noted in 3 of the patients with patent ductus arteriosus. Two of the 3 had tricuspid atresia and the third was a mongolian idiot with a ventricular septal defect as

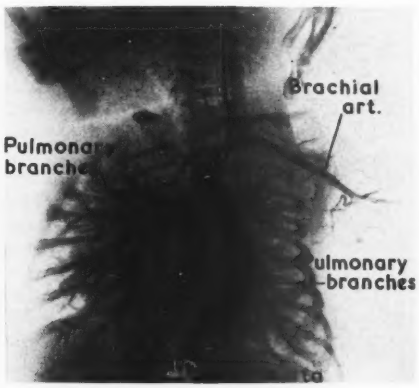

FIG. 3. G. W., age 10 days. Patent ductus arteriosus. The pulmonary artery is shown filling from the aorta.

well. A ninth case of patent ductus was included in the table. This infant was operated on and the presence of the ductus confirmed. No aortogram was performed on that particular baby because a continuous murmur could readily be heard in the pulmonary area.

In table 1, a summary of the findings in one case of persistent truncus arteriosus studied by aortography is also recorded. It was interesting that the pulmonary vessels filled from the aorta, in the aortogram, and the condition was confused with a patent ductus at the time. At postmortem, at a later date, the true diagnosis was made. A clearer picture might have been obtained had the left arm been used, since by this method it is possible

TABLE 1.—*Cases of Patent Ductus and Coarctation of the Aorta Shown by Aortogram*

	Name	Sex	Age	Diagnosis	Signs & Symptoms	Murmur	Heart Enlargement	Aortogram	Comment
1.	G.B.	F.	10 days	Patent ductus; tricuspid atresia	Cyanosis	1. Continuous in pul. area, 2. Systolic in 4th space.	Slight	Pulmonary vessels filled from aorta.	Necropsy. Diagnosis confirmed.
2.	G.W.	F.	10 days	Patent ductus; V.S. defect	None	Systolic in 2nd, 3rd and 4th spaces.	Slight	Pulmonary vessels filled from aorta	Associated V.S. defect fect. Mongol
3.	F.H.	M.	3 wks.	Patent ductus; Tricuspid atresia	Cyanosis	No murmur	Slight	Pulmonary vessels filled from aorta, and ductus itself was clearly outlined.	Necropsy. Diagnosis confirmed.
4.	R.G.	M.	2 mos.	Patent ductus	None	No murmur	Moderate	Pulmonary vessels filled from aorta.	—
5.	R.N.	M.	6 wks.	Patent ductus	None	Systolic in 2nd and 3rd spaces.	Moderate	Pulmonary vessels filled from aorta.	Died. No necropsy.
6.	R.R.	M.	3 mos.	Patent ductus	Heart failure	Systolic and early diastolic in pul. area	Gross	Pulmonary vessels filled from aorta.	Large ductus ligated at 3 mos. Cured.
7.	S.T.	F.	8 mos.	Patent ductus	Heart failure	Systolic and early diastolic in pul. area.	Gross	Pulmonary vessels filled from aorta.	Large ductus ligated at 8 mos. Heart failure. Cured.
8.	K.G.	F.	15 mos.	Patent ductus	Heart failure	Systolic thrill. Continuous murmur in pulmonary area.	Gross	Pulmonary vessels filled from aorta.	Large ductus ligated at 15 mos. Heart failure. Cured.
9.	B.K.	F.	14 mos.	Patent ductus	Heart failure	Continuous murmur in pulmonary area.	Gross	Aortogram not done.	Large ductus ligated at 14 mos. Heart failure. Cured.
10.	C.H.	F.	5 wks.	Persistent truncus arteriosus	Heart failure	Systolic in pulmonary area.	Gross	Pulmonary vessels filled from aorta.	Necropsy. Diagnosis confirmed.
11.	J.W.	M.	10 days.	Coarctation and common ventricle	Heart failure	Systolic in 2nd and 3rd spaces. Femoral arteries not palpable.	Moderate	Coarctation outlined distal to subclavian artery. (Adult-type)	Necrospy. Coarctation of aorta. Common ventricle. Aortic stenosis.

TABLE 1.—*Continued*

	Name	Sex	Age	Diagnosis	Signs & Symptoms	Murmur	Heart Enlargement	Aortogram	Comment
12.	K.C.	M.	2½ yrs.	Coarctation; V.S. defect; Patent ductus	None	Systolic murmur in 4th space. Arteries not palpable.	Moderate	Coarctation outlined distal to subclavian artery. No clear evidence of ductus. (Adult-type)	At operation patent ductus ligated. No repair of coarctation attempted.
13.	A.S.	M.	7 mos.	Coarctation and (?) associated defect.	None	Systolic murmur between scapulae and in mitral area. Femoral arteries not palpable.	Moderate	Coarctation outlined distal to subclavian artery. (Adult-type)	
14.	J.McD.	F.	1 wk.	Coarctation of aorta (infantile); Dextraposition of aorta; V.S. defect	None	Faint systolic murmur between apex and sternum.	Moderate	Coarctation distal to left subclavian artery (Infantile type) Ductus was patent but not shown	Died at 2 wks. Patent ductus was continuous with descending aorta distal to coarctation.

to outline the aorta more completely, as well as the pulmonary artery and branches, and thus identify the site of origin of the abnormal flow.

In 4 cases it was possible to demonstrate a coarctation of the aorta by the aortogram. (See fig. 4.) In none of these children were the femoral arteries palpable. In the older child no blood pressure readings were obtainable in the leg, and in the arm the blood pressure reading was 125/80. All had moderate cardiac enlargement and none were considered to be cases of pure coarctation. The presence of coarctation was proved at postmortem examination in 2 babies, and at operation in a third. The fourth has not been operated on yet.

DISCUSSION

The method of aortography which has been described appears to be a reliable one for demonstrating the presence or absence of a patent ductus arteriosus, provided the ductus is filling from the aorta as was the case in 8 of the infants studied. In one patient with coarctation a ductus was delivering blood from the right ventricle and pulmonary artery into the aorta, hence there was no reflux into the ductus and its patency was not evident by angiocardiography.

It may be difficult at times to eliminate the possibility of a persistent truncus by this method, but there are certain features that help to differentiate the two conditions. When the ductus fills from the pulmonary artery, the latter usually shows as a large vessel close to the aorta. On the other hand, the vessels arising from the aorta, in persistent truncus, are apt to be smaller than the main pulmonary artery. In persistent truncus, one may detect that the vessels going to the lung arise from

the ascending aorta and in this way be able to distinguish them from the ductus which arises from the descending aorta. In most instances, persistent truncus is accompanied by cyanosis, while patent ductus arteriosus is not.

There are both academic and practical reasons for studying patency of the ductus arteriosus in early life. From the academic point of view, it is of interest to know whether the finding by Barclay and associates,[1] of closure of the ductus in the first few moments of life in the lamb is applicable to man. Our work does not shed much light on this point since we have not had an opportunity to do angiograms in the first few moments of life. However, we have studied 2 patients each 5 days old, who had no evidence of patency of the ductus. According to Patten[3] the human ductus closes anatomically between the seventh and ninth week of life. The absence of patency in 2 infants under this age indicates that closure had already taken place in these instances at least.

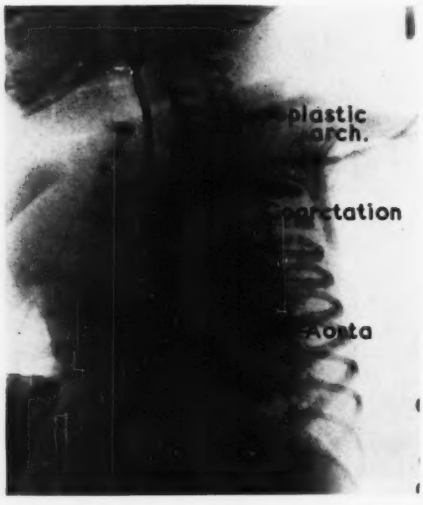

FIG. 4. J. W., age 10 days. Coarctation of the aorta. Marked constriction of the aorta is shown.

Another aspect of the problem of the early closure of the ductus in man, concerns the presence or absence of murmurs in the neonatal period. We have observed 3 babies in the newborn period who have had the typical continuous murmur of patent ductus. Two of these were premature infants. In one case the murmur disappeared as the baby grew older, and in the other, the baby died and the tetralogy of Fallot was found with a patent ductus postmortem. It would appear to be of significance that a continuous murmur was heard in these premature babies since this leads one to the conclusion that the normal absence of murmurs in healthy infants, during the neonatal period, is in favor of the belief that the ductus closes functionally at birth.

We have been able to study the relationship of the presence or absence of murmurs to patency of the ductus arteriosus by using the angiogram. Out of 9 cases of proved patency of the ductus, a typically continuous murmur was present in 3; in 2 the murmur occurred in systole and at times could be heard in early diastole; in 2 a systolic murmur only was heard in the pulmonary area; in 2 no murmur was noted at all. Thus one can have a variety of murmurs or none at all, and still have a patent ductus. A murmur does not depend on the degree of difference in pressure between the aorta and the pulmonary artery, because in the infant who had no murmur a great difference in pressure existed, since there was tricuspid atresia and a very small opening into the vestigial right ventricle. Furthermore the pulmonary artery was hypoplastic. Postmortem examination suggested that the absence of murmur in the pulmonary area, in this case, was probably due to the unusual length of the ductus. It was at least 12 mm. in length.

In infants, a murmur heard in the pulmonary area, lasting through systole and appearing to extend into early diastole is probably due to patent ductus arteriosus. A systolic murmur alone in the pulmonary area, in an infant, could be caused by a variety of congenital defects but patent ductus is the commonest. Functional murmurs must always be eliminated.

The practical importance of early diagnosis of patent ductus is emphasized by our findings of 4 cases, who in early life required operation. The diagnosis was suspected on clinical examination in each case. The angiogram confirmed

the diagnosis in the 3 cases where the diagnosis was not sufficiently clear-cut to recommend operation without it. All 4 patients recovered satisfactorily from the operation thus demonstrating that the ductus can be treated surgically in the first 15 months of life and even as young as 3 months of age, when cardiac failure makes operation imperative.

The clinical findings of these 4 cases are summarized in the table. All had murmurs in the pulmonary area. In 2 there was a continuous murmur and in 2 a systolic murmur was questionably prolonged into early diastole.

We have not included the many cases of patent ductus diagnosed by their murmurs alone and who had no other signs and symptoms. Such infants have little or no enlargement of the heart as a rule. The 4 cases under discussion had grossly enlarged hearts, enlarged to a degree that suggested the presence of some other associated anomaly of the heart. A very large ductus was found in each case. They all improved after operation and the murmurs disappeared. No specific evidence of another anomaly has been found yet, but further observations over the years may reveal a second defect.

In the 4 cases with failure, all had a rapid respiratory rate of 60 to 80 per minute. The liver was enlarged in all and 2 had rales in the chest. On administration of Digoxin, 2 showed improvement of their heart failure before operation. In all, the signs of failure cleared up rapidly after operation. X-ray films made before and after ligation of the ductus showed marked diminution in heart size over a period of three or four months. From the preoperative size of the heart in these infants and from their course before operation, there seems to be little doubt now that surgery was a life-saving measure.

Of the 4 cases of coarctation of the aorta presented in table 1, 3 were of the adult type. The fourth had a patent ductus that was delivering blood into the aorta. Our interest is primarily in the first 3, since they are amenable to surgery. Out of the 13 cases of coarctation recognized in the first year of life and coming to necropsy at this hospital in the past 10 years, 3 were of the adult type. For this reason we should search carefully for evidence of this anomaly, especially in infants whose hearts are enlarged, and who might thus require surgery at an early age. However, the average case of coarctation of the aorta is symptom-free until late childhood or adult life.

Palpation of the femoral artery is the most important clinical lead to the diagnosis and should be part of any examination of the heart. The diagnosis is not as easily made in infants as in older children because the femoral artery may be difficult to feel even in a normal infant. Blood pressure readings in the arms and legs are not as accurate in infants, and there is no notching of the ribs seen in the x-ray film. Other congenital defects of the heart may be present which will make the diagnosis of coarctation extremely difficult. For these reasons it is felt that aortography has a valuable place in establishing an accurate diagnosis and in indicating the exact site of the narrowing of the aorta. Figure 4 indicates how clearly the coarctation can be outlined by this technic.

Summary

A method of visualizing the aorta of infants with contrast medium is described. It requires the introduction of a number 18 needle into the brachial artery and the rapid injection through it of 5 cc. of 35 per cent Diodrast solution. While the injection proceeds, serial x-rays are taken at the rate of three or four a second. The aorta is clearly outlined for approximately one second by this method. This has proved useful in demonstrating the ductus arteriosus, when it is patent, and coarctation of the aorta. A continuous murmur, a systolic murmur or no murmur at all was found in various patients with patent ductus arteriosus. Thus aortography has proved useful in making a diagnosis in doubtful or obscure cases.

The findings in 4 infants with patent ductus arteriosus are described. These infants had grossly enlarged hearts, all of them have had

serious heart failure due to the congenital anomaly. All 4 were operated on successfully.

Coarctation of the aorta can be clearly delineated by this method in infants.

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Aortic Length: Angiocardiographic Measurements

By CHARLES T. DOTTER, M.D., DOUGLAS J. ROBERTS, JR., B.A., AND ISRAEL STEINBERG, M.D.

Statistical analysis of measurement of aortic length made on 250 angiocardiograms indicates that arteriosclerosis, hypertension and syphilitic aortitis produce elongation of the aorta. Aortic length varies widely among normal individuals but is roughly ten times the caliber of the ascending aorta. Syphilitic aortitis produces disproportionate elongation of the ascending portion of the aorta as compared to arteriosclerosis or hypertension.

ANGIOCARDIOGRAPHY affords an accurate delineation of aortic form and contour during life; it allows measurement of aortic length and diameter. By means of measurements made upon angiocardiograms, it has been possible to determine the range in caliber of the normal and diseased aorta. In 1949, the results of measurement of the caliber of the normal thoracic aorta at four anatomically fixed points—midascending, transverse, descending and diaphragmatic—were reported.[1] Measurement of 100 normal aortas (including those with arteriosclerosis) indicated that the caliber (for all ages) of the midascending aorta ranged between 16 and 38 and averaged 28.6 mm. In a study of 51 patients with syphilitic aortitis,[2] the range for the same point of measurement was from 38 to 70 mm. and the average caliber was 45.4 mm.

No study of the length of the thoracic aorta, as measured during life, has been reported. The relationship of age, arteriosclerosis, syphilis and hypertension to aortic length has hitherto not been investigated. Accordingly, for academic as well as clinical reasons, the following angiocardiographic study of the length of the thoracic aorta was undertaken.

METHOD

The material for this study comprised 250 selected angiocardiograms. All were made in the left anterior oblique or left lateral projection so as to afford a side view of the thoracic aorta; all were exposed at a 72 inch target-film distance so as to minimize distortion and enlargement of the aorta and secure a film comparable to the standard chest film; all were made during suspended deep inspiration. Films selected were of a quality adequate to allow satisfactory measurement. Unfortunately, technical progress at the time most of the films were made did not allow for timing of exposure with respect to the phase of the cardiac cycle. Variations in the length of the aorta occurring between systole and diastole are probably not sufficient to render the results of this study invalid. Measurements of aortic length were made with a commercially obtained map measuring device which consisted of a small rotating wheel connected through a gear to a calibrated scale, attached to a handle. The small wheel was rolled along the desired aortic contour and the length read directly from the dial, thus effecting the duplicatable measurement of curved lines with a reasonable degree of accuracy.

The following four measurements were made (see fig. 5*B*):

Length of Thoracic Aorta. This measurement was made by determining the length of the outer border or contour of the thoracic aorta from the upper border of the anterior sinus of Valsalva to the point where the aorta passed through the left leaf of the diaphragm (fig. 5*B*, A to C). A smooth continuation of the aortic arch was carried through the points of origin of the brachiocephalic arteries in making this and the following measurement.

Length of Ascending Aorta. This length was measured, as above, from the sinus of Valsalva to the point of juncture of the posterior margin of the left subclavian artery with the aortic arch (fig. 5*B*, A to B). No attempt to measure the length of the transverse arch was made, this segment being included in the ascending and descending limb measurements.

Length of Descending Aorta. This length was measured, as above, from the left subclavian artery to the diaphragm (fig. 5*B*, B to C).

Caliber of Midascending Aorta. The maximum width of the midascending aortic lumen was determined, measurement being made perpendicular to

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This investigation was aided by grants from The Schering Corporation and The New York Heart Association.

the aortic walls with a centimeter rule (fig. 5*B*, line D).

Following measurement, all cases were classified into groups according to clinical data. Statistical analysis was applied to three major groups. (1) Eighty-four normal subjects in whom cardiac or aortic disease other than arteriosclerosis did not exist. (2) Fifty-one patients with syphilitic aortitis without aneurysm. (3) Twenty-six patients with hypertension. Eighty-nine patients were excluded from final analysis either because of other forms of heart disease (46 patients) or because of a positive serologic test for syphilis in the absence of evidence of aortic disease (43 patients). Too few cases of rheumatic heart disease or specific congenital lesions were available to warrant analysis. The statistical evaluation of results was conducted in accord with recognized procedure.[3]

Results

Normal Subjects, Including Those With Arteriosclerosis

The angiocardiograms of 84 cases were measured in which it could be reasonably certain on the basis of available data that no aortic disease other than atherosclerosis existed. No case with a positive serologic test for syphilis or with hypertension (above 140/90) was included. No case with rheumatic or congenital heart disease was considered acceptable, even though there was no evidence of aortic involvement. Arteriosclerosis was included in the normal group since, during life, it is impossible to exclude its presence, and since this condition is universally present in hospital patient material. Arteriosclerotic aortas were likewise included in the other groups studied. Average measurements as made in the three groups studied are presented in table 1.

Table 1.—*Mean Aortic Measurements in Normal (Including Arteriosclerotic), Syphilitic, and Hypertensive Patients*

Diagnosis	No. of Cases	Mean Age (Years)	Mean Length, Thoracic Aorta (cm.)	Mean Length, Ascending Aorta (cm.)	Mean Length, Descending Aorta (cm.)	Mean Caliber, Mid-Ascending Aorta (mm.)
Normal	84	42.8	33.2	12.4	20.8	32.3
Syphilitic aortitis	51	52.4	36.9	15.4	21.5	42.6
Hypertension	26	55.8	37.3	14.8	22.5	38.2

The 84 cases ranged in age from 9 to 74; the mean age was 42.8 years. The thoracic aorta ranged in length from 21 to 48 cm. with a mean length of 33.2 cm. The calculated standard deviation from this mean was ±5.07.

The thoracic aorta increases in length with age. The relationship between age and total length of the thoracic aorta is graphically presented in figure 1. By applying the method of "least squares," a formula for predicted aortic length was derived (*length* = 6.76 + 15.86 log_{10} *age*) and is shown as a smooth curve through the scattered individual plots from which it was derived. Thus, ideally, the aorta of a 30 year old patient should be 30 cm. in length; that of a 45 year old patient, 33 cm. *It is apparent from the wide scattering of individual observations that no precise numerical definition of the elongated aorta is warranted.* It was found that the aorta in males was usually slightly longer than in females.

An attempt was made to correlate the length of the ascending and descending limbs of the aorta. In youth, the ascending aorta composes about 33 per cent of the length of the thoracic aorta while as age and arteriosclerosis increase this percentage approaches 40 per cent. A wide variation in individual measurements was encountered, however, and it is believed that this ratio is of little statistical or diagnostic value. By comparing the values for aortic caliber and length, it was seen that the length of the thoracic aorta, roughly speaking, is ten times the caliber of its midascending limb. This relationship is significantly altered in the presence of syphilis of the aorta.

Patients with Syphilitic Aortitis

The angiocardiograms of 51 cases of syphilitic aortitis were subjected to measurement as described above. The age range for this group was 36 to 73 years, the mean age 52.4 years. The mean length of the thoracic aorta in this group was 36.9 cm., the increase in length as compared with the normal appearing mainly as an increase in length of the ascending limb. The caliber of the midascending

aorta was disproportionately increased (mean, 42.6 mm.) as compared with the increase in aortic length. In the presence of syphilitic aortitis, aortic length is usually less than ten times the midascending caliber, a point of potential diagnostic significance. Measurements of aortic length in syphilitic aortitis are plotted against age in figure 2, as is a curve expressing these points. In figure 4, the curves for normal, syphilitic and hypertensive aortic length are compared and indicate that both syphilis and hypertension add to the aortic elongation due to the aging process. Observation of the relative lengths of ascending and descending

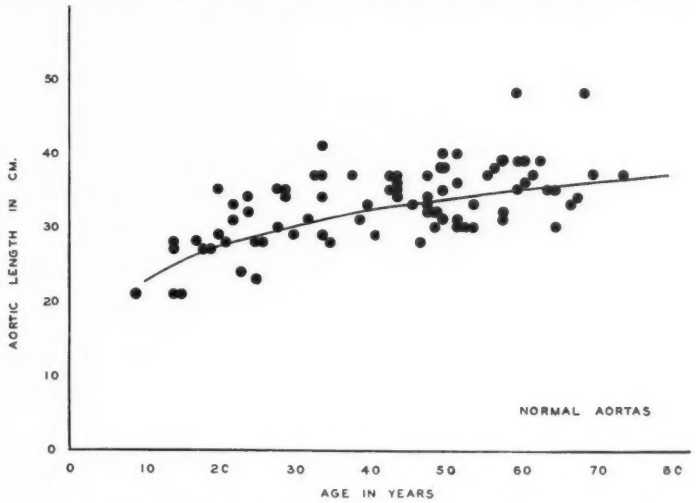


FIG. 1. Normal and arteriosclerotic group (84 cases). Length of thoracic aorta plotted against age. Predicted aortic length shown as solid black line. ($length = 6.76 + 15.86\ log_{10}\ age$).

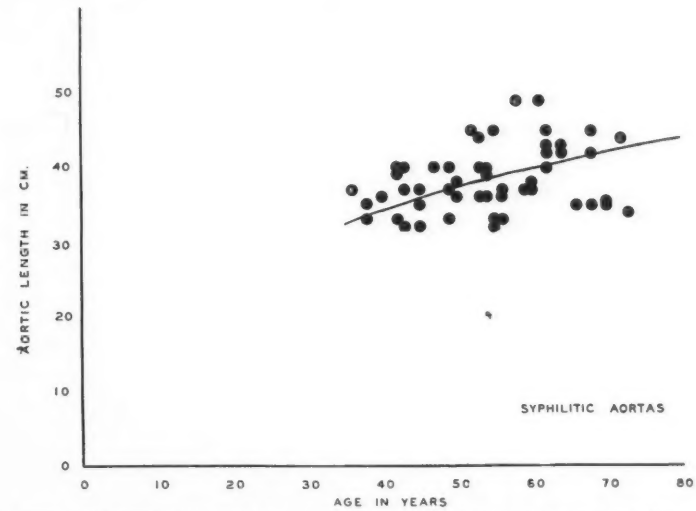


FIG. 2. Group with syphilitic aortitis (51 cases). Length of thoracic aorta plotted against age. Statistically derived curve expressing these measurements shown as solid black line.

limbs of the aorta in syphilitic aortitis shows a relatively greater increase in length of the ascending aorta as compared with the descending aorta. This is in keeping with the fact that syphilis affects the ascending aorta first and usually most severely.

Patients with Hypertension

Aortic measurements were made in 26 cases of hypertension (blood pressure greater than 140/90). The results are shown in table 1. Mean aortic length was comparable with that associated with syphilitic aortitis. The ob-

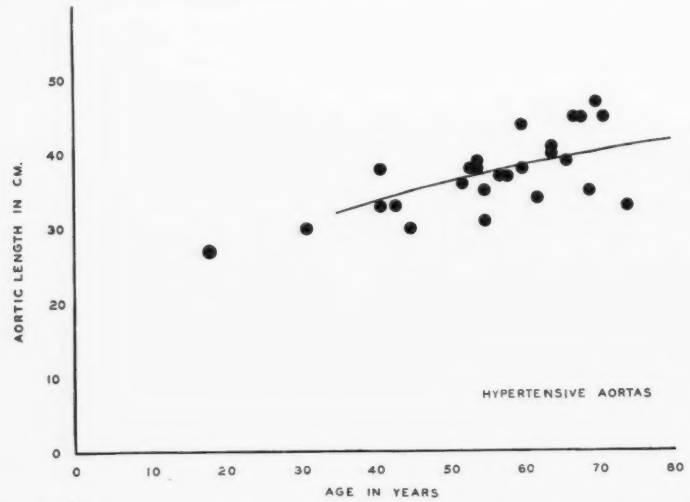


FIG. 3. Group with hypertension (26 cases). Length of thoracic aorta plotted against age. Statistically derived curve expressing these measurements shown as solid black line.

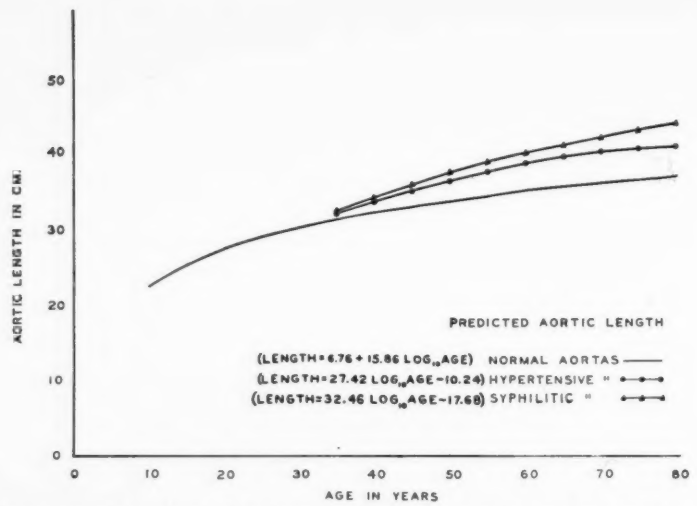
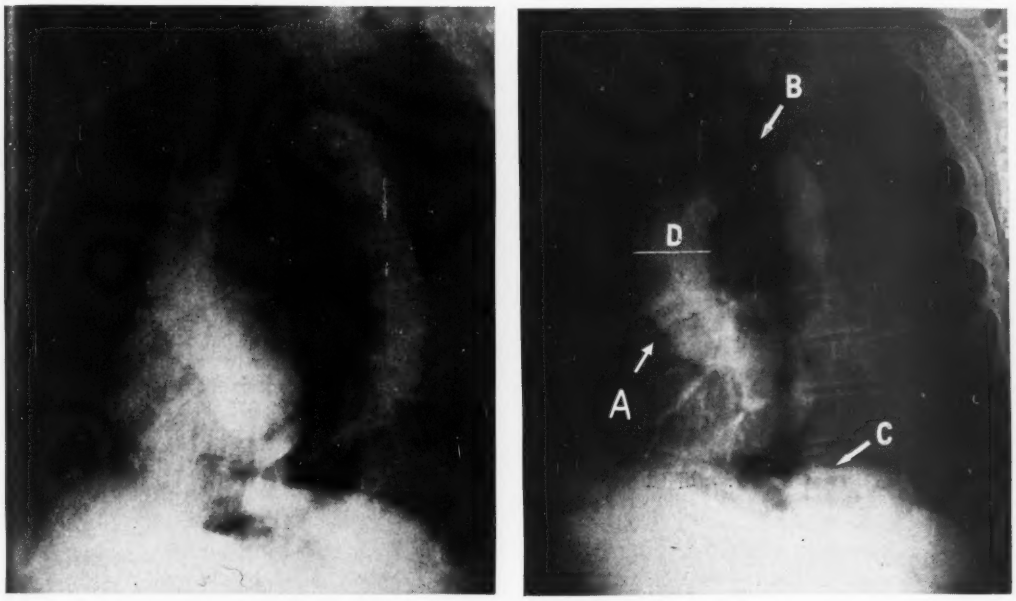


FIG. 4. Curves expressing observed comparative length of thoracic aorta in normal (plus arteriosclerotic), syphilitic and hypertensive groups.

served measurements of aortic length are plotted against age in figure 3 and a curve derived from these points is superimposed. The relative elongation of the aorta due to hypertension, syphilis and aging processes including arteriosclerosis is compared in figure 4. The caliber of the ascending aorta in the hypertensive group was not as great as that in the syphilitic group. In the hypertensive, as in the "normal" group, aortic length was about ten times the caliber of the ascending aorta.



A B

FIG. 5. Angiocardiograms, left anterior oblique projection, aorta opacified. *A*. (N.Y.H. #404 769) Hypertension; 68 year old male with blood pressure of 172/108. Aortic length, 45 cm.; ascending aortic length, 16 cm.; descending aortic length, 29 cm.; caliber, midascending aorta, 39 mm. *B* (N.Y.H.) #511 373) Syphilitic aortitis; 56 year old male with blood pressure of 135/75. Aortic length, 36 cm., ascending aortic length, 16 cm.; descending aortic length, 20 cm.; caliber, midascending aorta, 45 mm. Sites of measurements indicated as described in text.

DISCUSSION

The measurements herein presented allow certain generalizations. It is apparent that normal length of the thoracic aorta covers a fairly wide range. It follows that knowledge of the aortic length in a given instance cannot be expected to be of significant diagnostic value. Both syphilitic aortitis and hypertension produce elongation of the aorta; in each instance the elongation adds to that produced by age (and arteriosclerosis). In figure 5 are shown the angiocardiograms and aortic measurements in the following cases: *A*. a 68 year old man with hypertension and moderate arteriosIce-rotic elongation of the aorta and *B*. a 56 year old man with syphilitic aortitis.

A formula has been derived to express the probable length of the aorta at any age in the absence of disease other than arteriosclerosis. Despite a wide range of normal variation, this formula may serve as a base-line for the evaluation of aortic length. In a given case, knowledge of the total length of the thoracic aorta is of no value in the differentiation between syphilitic, hypertensive and arteriosclerotic aortic disease, although an abnormal relationship between the

limbs of the aorta in syphilitic aortitis shows a relatively greater increase in length of the ascending aorta as compared with the descending aorta. This is in keeping with the fact that syphilis affects the ascending aorta first and usually most severely.

Patients with Hypertension

Aortic measurements were made in 26 cases of hypertension (blood pressure greater than 140/90). The results are shown in table 1. Mean aortic length was comparable with that associated with syphilitic aortitis. The ob-

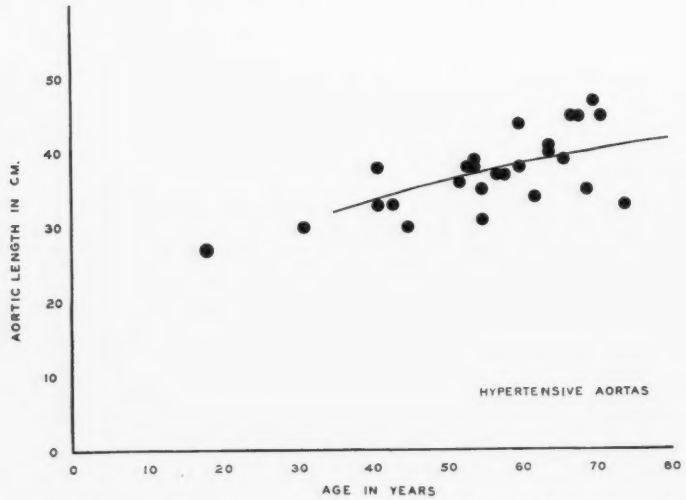


FIG. 3. Group with hypertension (26 cases). Length of thoracic aorta plotted against age. Statistically derived curve expressing these measurements shown as solid black line.

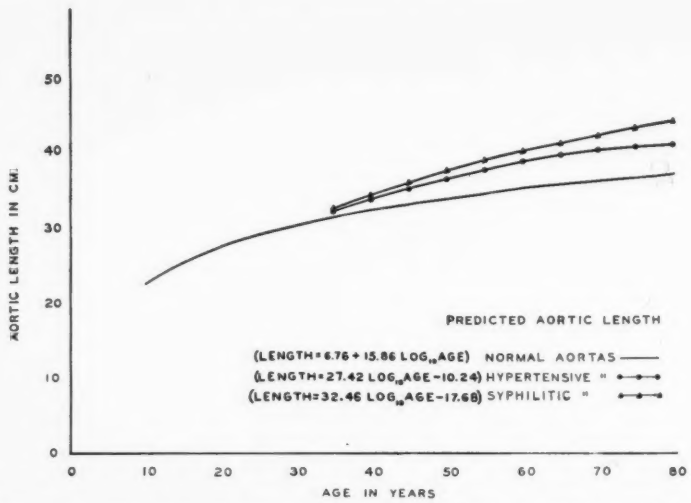
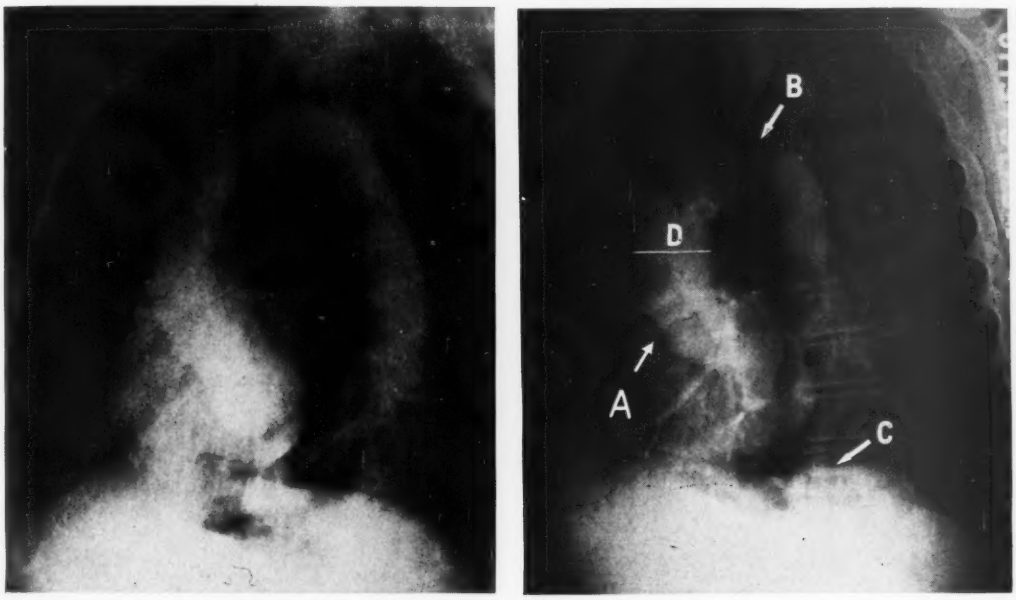


FIG. 4. Curves expressing observed comparative length of thoracic aorta in normal (plus arteriosclerotic), syphilitic and hypertensive groups.

served measurements of aortic length are plotted against age in figure 3 and a curve derived from these points is superimposed. The relative elongation of the aorta due to hypertension, syphilis and aging processes including arteriosclerosis is compared in figure 4. The caliber of the ascending aorta in the hypertensive group was not as great as that in the syphilitic group. In the hypertensive, as in the "normal" group, aortic length was about ten times the caliber of the ascending aorta.



A B

FIG. 5. Angiocardiograms, left anterior oblique projection, aorta opacified. *A*. (N.Y.H. #404 769) Hypertension; 68 year old male with blood pressure of 172/108. Aortic length, 45 cm.; ascending aortic length, 16 cm.; descending aortic length, 29 cm.; caliber, midascending aorta, 39 mm. *B* (N.Y.H.) #511 373) Syphilitic aortitis; 56 year old male with blood pressure of 135/75. Aortic length, 36 cm., ascending aortic length, 16 cm.; descending aortic length, 20 cm.; caliber, midascending aorta, 45 mm. Sites of measurements indicated as described in text.

DISCUSSION

The measurements herein presented allow certain generalizations. It is apparent that normal length of the thoracic aorta covers a fairly wide range. It follows that knowledge of the aortic length in a given instance cannot be expected to be of significant diagnostic value. Both syphilitic aortitis and hypertension produce elongation of the aorta; in each instance the elongation adds to that produced by age (and arteriosclerosis). In figure 5 are shown the angiocardiograms and aortic measurements in the following cases: *A*. a 68 year old man with hypertension and moderate arteriosclerotic elongation of the aorta and *B*. a 56 year old man with syphilitic aortitis.

A formula has been derived to express the probable length of the aorta at any age in the absence of disease other than arteriosclerosis. Despite a wide range of normal variation, this formula may serve as a base-line for the evaluation of aortic length. In a given case, knowledge of the total length of the thoracic aorta is of no value in the differentiation between syphilitic, hypertensive and arteriosclerotic aortic disease, although an abnormal relationship between the

caliber and length of the ascending as compared with the thoracic aorta may suggest the presence of syphilitic aortitis.

Uncounted variables exist which have not been taken into consideration in this study. Aortic length probably varies significantly with body habitus. It would not be surprising to learn that the ectomorph has a longer aorta than the mesomorph. No correlation with weight, height, surface area or other anthropometric measurements was possible because of the limited number of cases available for study.

Conclusions

1. An angiocardiographic study of the length of the thoracic aorta has been made and the results presented in: (a) 84 cases without aortic disease other than arteriosclerosis; (b) 51 cases of syphilitic aortitis; (c) 26 cases of hypertension.

2. Age, arteriosclerosis, syphilis and hypertension all appear to produce aortic elongation and are additive in this respect.

3. Syphilitic aortitis produces disproportionate elongation and dilatation of the ascending portion of the aorta as compared with arteriosclerosis or hypertension. This fact is of significance in the angiocardiographic diagnosis of syphilitic aortitis.

4. In the absence of aortic disease other than arteriosclerosis, the length of the thoracic aorta may be roughly predicted from the following formula: $length = 6.76 + 15.86\ log_{10}\ age$. A wide variation from this curve occurs normally, the standard deviation from the mean length being ± 5.07.

Acknowledgment

The authors wish to express their gratitude to Mr. Charles B. Aiken for his assistance in deriving the formula for predicted aortic length.

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The Nature of the RS-T Segment Displacement as Studied with Esophageal Leads

III. The Effects of Digitalis

By Avery A. Sandberg, M.D., Leonard Scherlis, M.D., Arthur Grishman, M.D., and Joseph Wener, M.D.

The electrocardiographic changes, with particular reference to the RS-T segment and T wave, in surface leads and in esophageal leads reflecting left ventricular cavity potentials, are studied in 7 persons with and without heart disease, before and after the administration of digitoxin. After the administration of digitoxin, the RS-T segment depression in precordial leads and in esophageal leads reflecting the potentials of the posterior surface of the left ventricle, are regularly associated with RS-T segment elevation in esophageal leads reflecting left ventricular cavity potentials. The possible roles played by myocardial involvement due to digitalis, modification of the monophasic curves, and the reduction of the human ventricular gradient are discussed.

CHANGES in electrocardiograms of animals and humans induced by digitalis were reported upon shortly after introduction of the string galvanometer,[1, 2] but it was not until the publications of Cohn and coworkers[3–5] that the significance of the T wave alterations due to digitalis was emphasized. Subsequently, other investigators published their observations of the changes in the T wave and RS-T segment in the three standard leads in both normal and diseased hearts, using varying doses and different preparations of digitalis.[6–8] A regular sequence of changes in the T wave and RS-T segment induced by digitalis was described by McMillan and Bellet in 1932.[9] These changes consisted essentially of progressive lowering of the height of the T wave with subsequent depression of the RS-T segment, and finally diphasic or inverted T waves. These authors also observed that smaller doses of digitalis were required to produce T-wave and RS-T segment changes in the electrocardiograms of older persons, especially with diseased hearts, than in young persons.[10] The electrocardiographic changes in the precordial leads due to digitalis have been described in several reports.[11–13]

The significance and nature of the T wave and RS-T segment alterations due to digitalis have been the subject of much controversy. The demonstration of myocardial damage in animals following the administration of very large doses of digitalis[14–18] has served to support the school of investigators ascribing the changes in the T wave and RS-T segment to myocardial involvement,[19–21] with possible resultant delay in conduction.[19, 20] Other authors ascribe the RS-T segment and T wave changes to modification in the form of the monophasic curves[22, 23] or to a reduction of the human ventricular gradient towards a more normal level.[24]

Though the changes in the T wave and RS-T segment due to digitalis have been adequately described for surface leads, only a few observations have appeared as to the nature of the electrocardiographic changes occurring within the ventricular cavities.[13, 21] Because of the anatomic relationship and proximity of the esophagus to the left atrium and ventricle, esophageal electrocardiography affords a readily available method for the study of potentials of the human left ventricular cavity* and posterior left ventricular surface. In previous studies it has been demonstrated that eso-

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* It is recognized that the potential of the left atrium does not necessarily reflect exactly the potential of the cavity of the left ventricle.

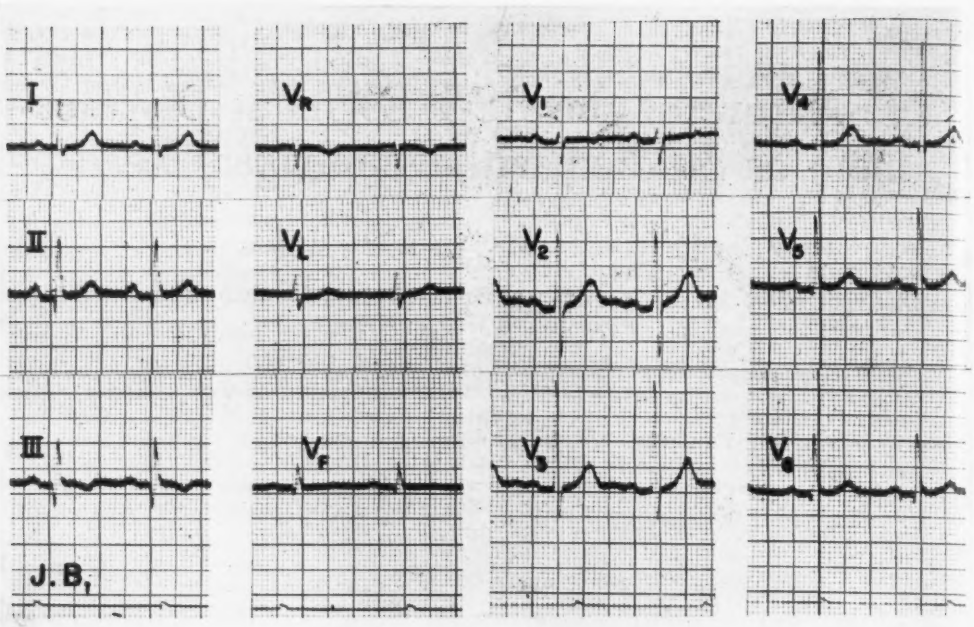

FIG. 1*A*. J. B. 54 year old man with hypertensive heart disease. Records were taken prior to digitoxin administration. (All records were taken at 1 mv. = 10 mm. sensitivity.) All electrocardiograms were recorded simultaneously.

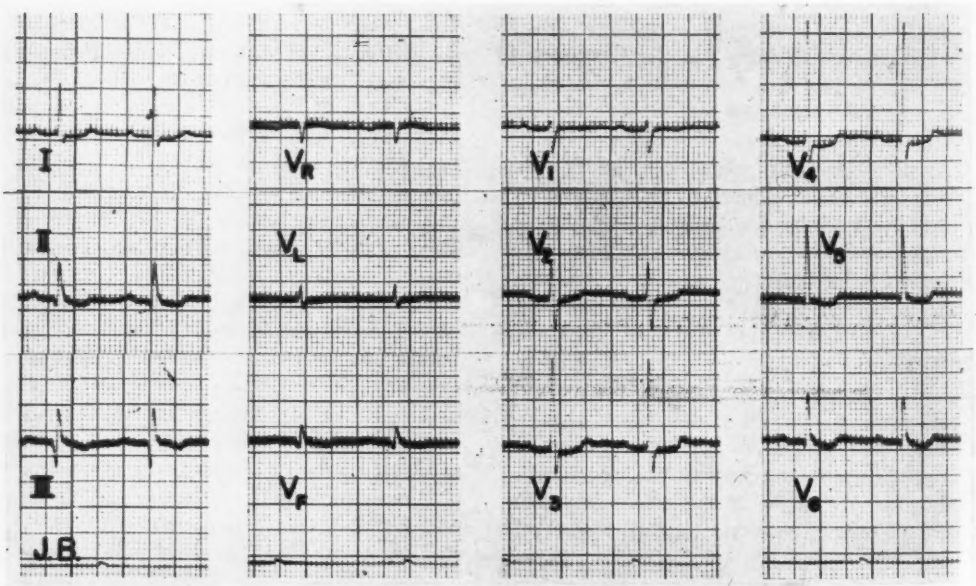

FIG. 1*B*. Records were taken after the administration of 3.2 mg. of digitoxin. Note RS-T segment depression in Leads I, II, V_L, V_F, and V_1 through V_6. RS-T segment is slightly elevated in V_R. Note striking T-wave alteration as compared with control record 1*A*.

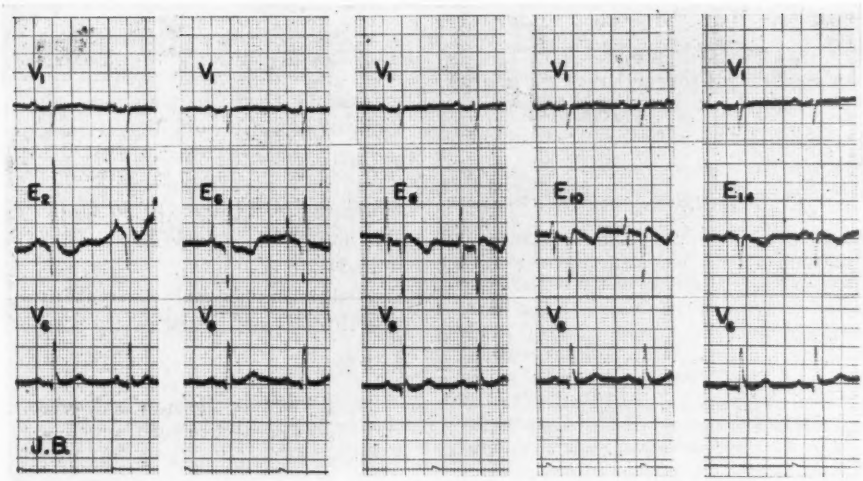

FIG. 2A. Esophageal electrocardiograms recorded prior to the administration of digitoxin to patient J.B. E_2 is recorded at lower esophageal level. E_8 and E_{10} are recorded at left atrial level and reflect left ventricular cavity potentials. Note presence of intrinsic atrial deflection. E_{14} is recorded at supracardiac level.

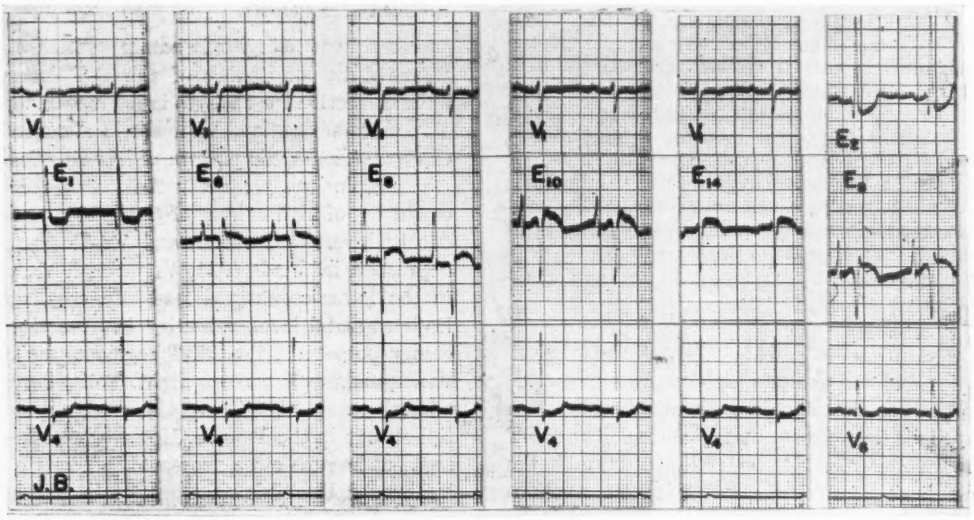

FIG. 2B. Esophageal electrocardiograms recorded subsequent to digitoxin administration. RS-T segment is depressed in E_1 and E_2 and markedly elevated in E_8 and E_{10}. Note changes in T-wave contour.

phageal electrocardiograms recorded at certain atrial levels reflect RS-T segment changes occurring within the left ventricular cavity.[25] This level is characterized by the recording of a ventricular QS or Qr pattern accompanied by an intrinsic atrial deflection.[26] Similar ventricular patterns have been obtained with catheters placed inside the human and animal left ven-

tricular cavity.[27–29] In the present study, the simultaneous recording of esophageal leads with standard and unipolar extremity and precordial leads was employed to investigate the nature of RS-T segment and T wave changes due to digitalis.

Methods

The method of recording multiple esophageal electrocardiograms has been described in more detail elsewhere.[25] In brief, it consists of the introduction of an esophageal electrode containing 15 fine wires, each separately connected to external metal bands 1.75 cm. apart. An electrocardiogram was recorded at each of these fifteen levels before and after the administration of digitoxin, Lead E_1 reflecting left posterior ventricular surface and E_{15} reflecting the supraatrial level. Three electrocardiograms were recorded simultaneously, the selected esophageal electrocardiogram being recorded with any desired combination of precordial or other esophageal leads. The three standard leads, V_R, V_L, V_F, and six unipolar precordial leads were recorded before and after the administration of digitoxin.

Each patient was given 1.2 mg. of digitoxin as an initial oral dose, followed by the administration of 0.2 three times a day or 0.1 mg. four times a day until toxic symptoms or electrocardiographic changes appeared. In no case was the above dosage maintained for longer than seven days.

The group of patients studied consisted of 3 young persons with no evidence of heart disease, and 4 patients with various degrees of cardiac enlargement. The latter group included 1 patient with rheumatic aortic stenosis and 3 patients with essential hypertension. None of these patients had taken any digitalis preparation previously, nor were there any symptoms of angina pectoris or cardiac decompensation.

Results

In 3 of the patients with cardiac disease the electrocardiograms before the administration of digitoxin were essentially normal. The RS-T segments recorded in precordial leads and in the esophageal leads at the posterior left ventricular surface and at atrial level were isoelectric. In these 3 patients the following electrocardiographic changes occurred after the administration of 3.0 to 3.2 mg. of digitoxin:

1. *RS-T Segment.*

Depression of the segments occurred in Leads I and II, precordial leads V_1 through V_6 (figs. 1*A* and 1*B*), and in lower esophageal leads (E_1 to E_4) reflecting posterior left ventricular surface potentials (figs. 2*A* and 2*B*; only E_1 and E_2 shown). The depression was most marked in Leads V_4 through V_6 and in the lower esophageal leads. Elevation of the RS-T segment occurred in esophageal leads E_7 through E_{10} at atrial level (only E_8 and E_{10} shown in figs. 2*A* and 2*B*), in supraatrial leads E_{12} through E_{15} (only E_{14} shown in figs. 2*A* and 2*B*) and in Lead V_R. The elevation was most marked in esophageal leads at atrial levels reflecting left ventricular cavity potentials.

2. *T Waves.*

The T waves in the standard, precordial and lower esophageal leads became markedly diminished in amplitude, or diphasic (minus-plus) in contour. In esophageal leads reflecting left ventricular cavity potentials the T waves, which had been inverted prior to the administration of digitoxin, became diphasic (plus-minus) in configuration.

3. *The Q-T Intervals.*

Subsequent to digitoxin administration there was definite shortening of the Q-T interval after correction for changes in heart rate.

In the one patient with aortic stenosis an electrocardiographic pattern of left ventricular hypertrophy was present in the control record, consisting of high voltage of the QRS complex, deeply inverted T waves and RS-T segment depression in Leads I, II, V_3 through V_6, and in the lower esophageal leads. In esophageal leads at atrial level, reflecting left ventricular cavity potentials, the RS-T segment was elevated and the T wave upright. Following the administration of digitoxin, there was no essential change in the T wave. However, the RS-T segment became more depressed in Leads I, II V_3 through V_6 and lower esophageal leads, and more elevated in esophageal leads at atrial level. The Q-T interval became shortened.

In 3 patients without any evidence of heart disease, only minimal lowering of the T waves occurred in the surface leads following digitoxin administration. No significant RS-T segment alterations were noted.

In no instance was the RS-T segment depressed in esophageal leads at atrial level re-

flecting left ventricular cavity potentials either before or after digitoxin administration, nor were there any changes noted in the configuration or duration of the QRS complex.

Discussion

From the data which have been presented it is apparent that following the administration of digitoxin the RS-T segment depressions in standard, precordial and lower esophageal leads —the latter reflecting posterior left ventricular surface potentials—were regularly associated with RS-T segment elevation in esophageal leads reflecting left ventricular cavity potentials. The proximity of the esophageal leads at atrial level to left ventricular cavity potentials, and at lower esophageal levels to the posterior surface of the left ventricle, probably accounts for the more marked RS-T changes seen in these leads. The T wave changes in esophageal leads reflecting left ventricular cavity potentials were the opposite of those seen in precordial and lower esophageal leads.

Digitalis in the doses administered had no effect on the configuration or duration of the QRS complex. The persistence after digitalis administration of the ventricular QS or Qr pattern at left atrial levels, representing left ventricular cavity potentials, would indicate that conduction in the left bundle branches remained normal, since delay in conduction in the left bundle branch would be accompanied by initial positivity in the left ventricular cavity.[29, 30] Hence, digitalis did not affect the process of depolarization or conduction in the bundle branches in the present study.

Various investigators have demonstrated that injury to the endocardial aspect of the heart produces depression of the RS-T segment in epicardial leads and elevation of the RS-T segment in intracavity leads.[31, 32] It has also been shown that spontaneous or induced coronary insufficiency affects preponderantly the subendocardial myocardium[33–35] with resultant RS-T segment depression in left precordial leads. It has also been shown by us that in induced coronary insufficiency, the RS-T segment elevation in esophageal leads reflecting left ventricular cavity potentials probably indicates predominant involvement of the subendocardium.[25]

The administration of very large doses of digitalis preparations to animals has produced myocardial damage, which was reported by Büchner[14] and by Dearing, Barnes and Essex[17] as being chiefly localized to the subendocardium. Some investigators have attributed the electrocardiographic changes produced by digitalis to myocardial involvement, mainly univentricular in localization,[14] as a possible result of reduced coronary blood flow.[14, 19, 20] From the observation of McMillan and Bellet[10] and from the data of the present investigation it is apparent that electrocardiographic alterations due to digitalis are much more readily produced in older persons with diseased hearts than in normal young persons. Whether digitalis further aggravates an already damaged myocardium in patients with or without coronary artery disease is difficult to evaluate. It is interesting to note that "coronary" contour of the T wave may be produced by digitalis in diseased hearts.[9] Also, of some importance may be the fact that RS-T segment changes, similar to those seen in coronary insufficiency, have been observed in normal persons following exercise subsequent to the administration of digitalis, although absent prior to digitalis.[36] Whether all these changes are due to the direct action of digitalis on the myocardium[37] or result from a reduction of coronary blood flow because of vagal effects is not definitely known.[38–42] Anatomic lesions following therapeutic doses of digitalis have not been observed in the human or animal heart.[43, 44] It is conceivable that digitalis produces a gradient of myocardial involvement with therapeutic doses causing a biochemical or electrolytic disturbance[45, 46] rather than histologic alteration of the subendocardium. In the present study the RS-T segment became depressed in the precordial leads and in the lower esophageal leads reflecting the posterior surface of the left ventricle and became elevated in esophageal leads reflecting left ventricular cavity potentials following digitalis administration. The RS-T segments had been isoelectric prior to the digitalis. The RS-T segment in Lead V_R became elevated subsequent to digitalis administration. Similar

elevations in Lead V_R have been noted in coronary insufficiency[26, 47] and may be seen in published records following digitalis therapy.[48] Since Lead V_R usually represents predominantly ventricular cavity potentials the RS-T segment deviations are probably similar to those occurring within the ventricular cavities. The above findings, in accord with those of others, indicate that digitalis may produce myocardial involvement affecting predominantly the subendocardial aspect of the heart.

Some authors have attributed the RS-T segment and T wave changes following digitalis administration to modification of the monophasic action potential curves.[22, 23, 49] These authors believe that the electrocardiogram is a resultant of two monophasic curves, which because of digitalis effects lost their plateau component, with the curves becoming shorter in duration. This would indicate that the repolarization process occurs much more rapidly. Some investigators state that this is especially evident in the endocardial component of the monophasic curves.[49] These concepts may help to explain the shortening of the Q-T interval and the peculiar configuration of the RS-T segment and T wave in the majority of the patients receiving digitalis (figs. 1 and 2). Although there is some experimental evidence to support the view that digitalis modifies the monophasic curves, some investigators have criticized this explanation, believing that the electrocardiographic changes due to digitalis are a result of myocardial damage.[19, 20]

Employing the concept of ventricular gradient as advanced by Wilson, Macleod, Barker and Johnston[50] it has been proposed by Ashman[24] that the RS-T segment and T wave changes due to digitalis are normal physiologic phenomena dependent upon the relative magnitude of the manifest mean area of the QRS complex (A_{QRS}) and of the ventricular gradient (G). In the human heart the presence of a ventricular gradient, which accounts for the upright T wave, is due to the lack of uniformity of the effective duration of the excited state between endocardium and epicardium, especially concerning the repolarization phase.[51] In all probability the repolarization process is normally slower in the endocardial than the epicardial aspect of the heart. Local variations in the uniformity of the effective duration of the excited state may lead to RS-T segment and T wave changes.[50, 51]

According to Ashman, digitalis tends to abolish the human ventricular gradient, so that the time-course of depolarization and repolarization of the cardiac regions is almost equalized. Following the administration of digitalis, the process of repolarization may be shortened most in regions in which it lasted longest,[52] with repolarization of the subendocardial aspect commencing before depolarization of the epicardial surface has been completed.[24]

Summary

1. Digitalis was administered to 7 patients with and without heart disease.

2. The electrocardiographic changes following digitalis consisted of depression of the RS-T segment in precordial and lower esophageal leads, the latter reflecting the posterior left ventricular surface.

3. The RS-T segment became elevated in esophageal leads, reflecting left ventricular cavity potentials, following digitalis administration.

4. The nature of these changes is discussed.

Acknowledgment

We wish to express our appreciation to Dr. Arthur M. Master for his cooperation in making this study possible.

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CLINICAL PROGRESS

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The Modern Treatment of Coronary Thrombosis with Myocardial Infarction

By IRVING S. WRIGHT, M.D.

Coronary thrombosis with myocardial infarction is an extremely serious disease to the individual and to the nation. It kills at least 200,000 persons a year and cripples unknown numbers. The modern treatment is herein outlined. Established therapy is reviewed and evaluated. The use and technics for the control of anticoagulant therapy are discussed.

CORONARY thrombosis kills at least 200,000 people a year in the United States, and this figure will increase inexorably as the average age of our population continues to increase. It occurs in all ages but is predominantly encountered in persons over the age of 40. In general, it may be said that coronary thrombosis occurs at an average age which is approximately 6 years younger in men than in women. More men than women suffer and die from it in every age group under the age of 80. It has been encountered in infants as young as 3 months. One of the most unfortunate characteristics of this disease is that it strikes down many persons at the height of their productive years and activity, at times when they have the greatest responsibilities toward their communities and their families. It is a problem of increasing importance in national and community life.

The underlying process responsible for this condition is almost invariably arteriosclerosis, frequently a special type of intimal atherosclerosis. There are rare instances in which narrowing of a coronary artery has occurred either as a result of some other disease process or as a congenital anomaly, or in which myocardial infarction has occurred as a result of overstrain without adequate blood supply to an area of the myocardium. But such situations are so infrequent that for purposes of this discussion they may be ignored. The usual sequence is that arteriosclerotic plaques narrow the lumen of the coronary artery to such a degree that a thrombosis eventually occurs. This in turn produces the sudden occlusion which results in marked ischemia of the muscle, with subsequent necrosis and a profound effect on the efficiency of the heart muscle. This may occur as a result of occlusion of a small branch of the coronary tree, in which case recovery is very likely to occur. On the other hand, it may be a very extensive process involving a large area of the myocardium (or a key area of the myocardium); in which case a very serious illness and even death may ensue. Death, however, may not be the result of the myocardial infarction per se. Complications and death are frequently the result of secondary thromboembolic phenomena rather than of the

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A fuller presentation of this material appeared in Veterans Administration Technical Bulletin TB 10-61. It is being presented in somewhat shorter form through the courtesy of the Veterans Administration.

original insult. These phenomena may include: (1) Subsequent extension of the original thrombus to block off additional arteries or branches of the artery which was primarily involved. (2) Involvement of some other branch of the coronary tree which further embarrasses the heart action. (3) The development of mural thrombi, attached to the endocardium at the location of the original infarction, which are capable of releasing emboli to various parts of the body, either from the right side or the left side of the heart depending upon the location of the mural thrombus. (4) The development of thromboses elsewhere in the body, particularly in the veins of the legs, which are in turn capable of producing fatal and nonfatal emboli.

Treatment, Other than with Anticoagulants

Curiously enough, until very recently, therapy has been directed for the most part in such a manner as to encourage the tendency to clot formation. Rest has been emphasized and has usually been accompanied by heavy sedation, in itself conducive to slowing of the blood flow and the development of thrombosis. While many forms of therapy have been recommended in the past, those which have stood the test of time and are still considered to be of value are as follows:

1. *Rest.* There is no question but that rest is essential in the treatment of this condition. A myocardial infarction goes through stages during which the initial anoxemia results in the development of necrosis. Thereafter it takes a considerable period of time for fibrosis and scarring, accompanied by development of a collateral circulation, to restore the muscle to anything like its former strength. In most instances it appears that necrosis is at its maximum about 10 days after the original infarction, and thereafter recovery takes place very slowly and depends to a considerable degree on the size and location of the infarction. It seems quite illogical therefore to place any strain on the heart muscle above minimal activity during the first three or, better, four weeks. If the infarction is large, or if there is evidence of cardiac embarrassment, this period may well be extended to from six to eight weeks. During this time the patient should be at bed rest. There is one exception to this ruling. There are many patients who have great difficulty in using the bed pan. It is the author's belief, and that of many others, that the use of a commode by the bedside, with the assistance of nurses and orderlies, may require much less effort on the part of the patient than the use of a bed pan. A commode is therefore recommended as soon as the patient appears to be able to make the short move from the bed which is required. Most patients are extremely grateful for this accommodation. After a period of from three to eight weeks, depending on the condition of the patient and the reaction of his pulse to the initiation of activity, he should begin to sit up in bed and exercise, using the arms and legs quietly at first. Finally, he is moved from the bed to a chair and gradually begins to assume increasing activity. The pulse is watched very carefully during this period. A pulse rate exceeding 100 means that exercise should be discontinued for the time being, to be started again after a period of rest. Dyspnea is also evidence that the patient should not force activity without further rest.

2. *Sedation.* Patients with coronary thrombosis usually suffer from marked apprehension and extreme nervousness, both at the time of their attack and subsequent to it. This cannot but aggravate the situation since the release of adrenaline and nervous stimuli tend to increase vasoconstriction. The sedatives of choice still remain morphine sulfate given in doses of 0.015 grams, the precise amount depending on the degree of pain suffered by the patient; Pantopon, 0.02 gram, appears to produce less nausea than does morphine in many people. These drugs are preferably given by hypodermic, because nausea is frequently present and an oral narcotic may not be adequately absorbed. Papaverine, 0.1 grams given intravenously, may also be administered for severe pain but sometimes produce disagreeable side reactions. As the pain decreases, other forms of sedation, such as Demerol or the barbiturate compounds, may be used as indicated. It is customary to use sedation and narcosis freely

during the first several days if the pain warrants it and thereafter to give only sufficient so that the patient is prevented from becoming apprehensive as a result of sensations of compression or pain.

3. *Alcohol.* Whiskey, or alcohol in other forms, may be used freely. Its benefits may be due to its vasodilating effects or to its sedative and relaxing action, but it frequently proves as effective as the opiates. A few patients become excited rather than relaxed by alcohol, and under such circumstances it is of course contraindicated. Alcohol so used should be regarded as a medication and the patient's tolerance, and the possible development of addiction to it, must be considered.

4. *Oxygen.* Oxygen is being used with increasing frequency in the treatment of myocardial infarction. It is especially indicated if there is evidence of appreciable pain, dyspnea, or cyanosis. It is important to watch the nail beds of a patient as well as his lips and face for evidence of cyanosis. One should not reserve oxygen for an emergency, or as a lifesaving procedure, but should give it freely so that the myocardium can be saved any unnecessary labor during the time when it is being repaired. When it is to be administered, the patient may be kept in an oxygen tent, or a mask may be used. If the dyspnea or cyanosis are extreme, concentrations up to 100 per cent should be used without hesitation. In very mild cases, its use may never be necessary.

5. *Infusion and Transfusions.* It is not uncommon for patients with coronary thrombosis and myocardial infarction to become dehydrated, either because they are not given sufficient fluids by mouth or because they are nauseated at the time of their admission. Furthermore, prolonged sedation and narcosis decrease the natural intake of fluid. If dehydration or shock are pronounced, 0.1 N saline infusions with 5 to 10 per cent glucose are indicated in quantities of 500 cc. Infusions of this nature however should be given *very slowly* in order to avoid imposing an additional strain upon the heart.

Gold, Prinzmetal, and others have shown that transfusions of plasma or whole blood are useful to combat shock in the care of these patients. Prinzmetal demonstrated in animals that, if the heart muscle is weak and herniating as a result of insufficient blood, the addition of fresh blood or plasma may reduce the tendency towards herniation within a very short time. The restoration of blood pressure and general tone which is observed in patients suggests that a not dissimilar procedure may take place in human beings, although this cannot be regarded as definitely established at present. When transfusions are given the amount should probably be not more than 250 to 300 cc. This procedure may be repeated in four hours. Whenever patients are receiving fluids intravenously they must be under continuous observation.

6. *Other Drugs.* In general, it is no longer considered good practice to give digitalis in the treatment of coronary thrombosis with myocardial infarction unless there is pronounced evidence of cardiac failure and the status appears to be deteriorating. The question has been debated widely but at present this position is regarded as justified. If digitalis is to be administered, it may be given in the form of extract of digitalis, powdered digitalis, digitoxin, or other glucosides having a similar action. The dosage should be sufficient to produce satisfactory digitalization but it is our impression that it is less hazardous to digitalize with moderate rapidity than by using a single massive dose.

Quinidine should be used in case of paroxysmal ventricular tachycardia. Some cardiologists also use it in the presence of evidence of cardiac irritability such as numerous premature beats. Under these circumstances, the dosage is 0.3 gram three to five times a day. In extreme conditions, this dosage may be doubled.

While aminophylline has been used the evidence that it has altered the mortality in any significant fashion is, in our opinion, inconclusive. If it is desired to administer it, with the hope that it will serve as a coronary vasodilator or for any other reason, it should be given in dosages of 0.25 gram intravenously every four to six hours. It should be administered slowly, preferably as a drip infusion in

100 cc. of a solution of sodium chloride or glucose in distilled water. There have been some fatalities resulting from the rapid injection of aminophylline in patients who were doubtless sensitive to the drug.

There have also been advocates of the use of atropine, 1 mg. every four hours, in the treatment of coronary thrombosis. Here, also, there is inconclusive evidence of a demonstrable beneficial effect. A definite indication for its use exists, however, when carotid sinus hypersensitivity is present.

The Use of Anticoagulants

1. *Experimental and Clinical Results.* As early as 1938, Solandt and Best reported animal experiments in which coronary thrombosis was produced by isolating the coronary artery and injecting sodium ricinoleate into its lumen. The injected material was kept in contact with the intima for 5 minutes and the clamps on the vessel were then released. Thrombosis developed in almost every case in which heparin was not used whereas, in a corresponding study in which heparin *was* used, it was almost never observed. Solandt, Nassim, and Best continued their studies by producing intracardiac mural thrombi and, in turn, preventing their formation by the administration of heparin. In these latter experiments, a technic was evolved by which large mural thrombi could be regularly reproduced in the lumen of the left ventricle: its endocardium was injured by injecting sodium ricinoleate, and the myocardium was damaged by ligating the anterior descending branch of the left coronary artery. When heparin was not used, there was rapid formation of a thrombus, but none was seen in those experiments in which heparin was given before the injury was produced. The results of these studies left no doubt that under certain experimental conditions the effect of heparin in preventing thrombosis could be readily demonstrated.

Following these studies, sporadic efforts were made to use heparin in the treatment of clinical coronary thrombosis but as far as is known no large, well-controlled series were conducted because of the difficulties of continued heparinization. The question of increasing hemorrhage in the intima was also raised, although more as a theoretic than a proved risk. Following the early clinical use of dicumarol, it was used in a few patients with coronary thrombosis and myocardial infarction. The author began the study of dicumarol in the treatment of coronary thrombosis during May, 1942. After three and one-half years of experience involving 80 patients, the following conclusions seemed warranted. The use of dicumarol had not aggravated the condition in any patient. It appeared physiologically sound to give anticoagulant therapy when (1) there was a tendency for propagation of the original thrombus, (2) multiple thrombi tended to form in the coronary arteries or elsewhere, and (3) one or more emboli had occurred. The thromboembolic processes appeared to have been interrupted. There was no evidence that thrombi, once formed, had been dissolved. The progression of established infarctions did not appear to be interrupted. The rate and rhythm of the heart was not directly affected. These results were reported in December, 1945. In January, 1946, Nichol and Page, who had been studying this problem during the same period as the author, published their experience with dicumarol in the treatment of acute coronary thrombosis. They reported results in 50 attacks occurring in 44 unselected patients observed between June, 1943 and October, 1945. Their results appeared to be favorable. In February of 1946, Peters, Guyther, and Brambel reported their experience with acute coronary thrombosis, and they also believed their results to be favorable. Following these early papers a series of other papers have appeared confirming these observations.

These series, however, were not sufficiently large or well-controlled to warrant detailed and final conclusions. The Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction was therefore established by the American Heart Association. This committee, on which the author served as chairman, was composed of teams in 16 leading hospitals in the United States; each team was headed by an outstanding cardiologist and included statisticians, chemists, and various consultants. A

total of 1,031 cases have been studied in detail and submitted to careful statistical analysis. Of these, 442 cases received excellent conventional treatment for coronary thrombosis with myocardial infarction, while 589 received the same treatment plus the addition of the anticoagulants heparin or dicumarol, or both. The majority of this latter group received dicumarol alone. The composition of the sample as to age, sex, and previous history was remarkably similar in the two groups.

Of those patients not receiving anticoagulant therapy, referred to hereafter as the control group, 23.4 per cent died. Of those who received anticoagulant therapy, referred to hereafter as the treated group, 16.0 per cent died. There was therefore a saving of life of approximately one-third in the group receiv ng anticoagulant therapy. This does not represent the full potential benefits of treatment, since careful analysis has shown that many of the patients who received anticoagulants did not receive what is now regarded as ideal anticoagulant therapy. When the cases were analyzed on the basis of deaths per week, it became clear that the control group showed a greater incidence of death each week up to and including the fourth. Thereafter, the deaths were so few that differences between the two were not statistically significant. Analyzed according to age, the control group showed a higher death rate than did the treated group in each series from those under 50 to those 70 or over. The difference was more pronounced in the older age groups and in those with one or more thromboembolic complications.

When the percentage of cases developing thromboembolic complications was examined, the following findings were noted. In the control group, 26.0 per cent developed one or more thromboembolic complications as compared with 10.9 per cent in the treated group. When the series was evaluated from the viewpoint of the average number of thromboembolic complications per hundred cases, it was found that there were 41.8 thromboembolic complications per hundred cases in the control group as against only 13.1 per hundred cases in the treated group. The number of thromboembolic complications of various types and locations per hundred cases in the control and treated groups showed a highly significant difference. Secondary myocardial extensions occurred in 9.7 per cent of the control group but only in 3.2 per cent of the treated group. New infarcts occurred in 6.1 per cent in the control as contrasted with 1.9 per cent in the treated group. Pulmonary emboli were encountered in 11.6 per cent in the controls against 4.8 per cent in the treated group. Cerebral emboli were diagnosed in 4.9 per cent of the controls but only in 0.7 per cent of the treated group. Peripheral emboli occurred in 2.7 per cent of the controls as compared with 0.5 per cent of the treated group. Venous thrombosis developed in 6.8 per cent of the control group and in 2.0 per cent of the treated group. The review of these figures, which will appear in the final report of the Committee on Anticoagulants, demonstrates conclusively that the administration of anticoagulants produces a marked reduction in death rate from coronary thrombosis and has an even greater effect in preventing thromboembolic complications. These complications cannot be regarded lightly since they leave some patients hopeless hemiplegics, others with the loss of one or more limbs by amputation, or with similarly serious disabilities.

In the light of these figures and of an extensive experience with the use of anticoagulants, it is difficult to avoid the conclusion that anticoagulants should be administered to every patient suffering from an acute coronary thrombosis unless the definite contraindications which will be subsequently mentioned are present. On the other hand, as is widely recognized, anticoagulant drugs are not without their hazards. They, like most other forms of medical treatment, require skill and knowledge of the technic for their use. The incidence of bleeding which occurred per hundred cases in the series under discussion should be considered. In the control group, episodes of bleeding occurred 5.9 times in each hundred cases. This incidence was a surprise to some physicians who had assumed that bleeding was an uncommon occurrence in coronary thrombosis. The episodes included hematuria, epistaxis, and numerous other minor evidences of bleeding. In the treated group, there were a total of 15.3 episodes per hundred

cases. Of these 15.3, 2.7 occurred before the anticoagulants had been administered, and 3.4 were believed to be due to causes other than anticoagulant administration; 9.2 were believed to be due to or aggravated by anticoagulant therapy. Hematuria was the most common example and should be watched for carefully in all cases receiving anticoagulant therapy. It occurred in 7 episodes per hundred cases of which 5.3 were microscopic and 1.7 gross. Hemoptysis occurred in 1.8 episodes per hundred cases in the control group and 3.2 in the treated group. Epistaxis occurred less than 0.2 times per hundred cases in the controls but 1.5 times per hundred cases in the treated group; other bleeding occurred 0.2 times per hundred in the control group and 1.0 in the treated group. There is, then, no question but that the incidence of bleeding is higher in the cases receiving anticoagulant therapy.

In the entire series, there were only 3 or possibly 4 patients who might be considered to have died as a result of bleeding associated with the use of anticoagulants. On the other hand, it would appear that 46 lives were saved. There is, therefore, a calculated risk in return for which the dividends, in terms of lifesaving and reduced disability, are high.

2. *Technic of Administration.* The following technic of administration is recommended in the case of heparin: it should be injected intravenously in doses of 50 to 75 mg. every four hours until the action of dicumarol is evident in terms of an effect upon prothrombin time. Administration should be controlled by use of the Lee-White test tube method for the determination of clotting time. No additional heparin should be given if the clotting time exceeds 20 minutes when measured prior to the next injection; it may be measured again in four to eight hours to determine if it has decreased to less than 20 minutes. Recently a heparin preparation in a retarding menstruum (Depo-Heparin) has been made available for intramuscular use. The author gives 300 mg. in the first dose and 200 mg. every 12 hours thereafter, always providing that the clotting time is less than 20 minutes before the next dose is administered.

Dicumarol should be administered as follows: Following a prothrombin determination which is within normal limits (12–18 seconds depending on the exact technic used; Quick, or Link-Shapiro modification of the Quick technic), an initial dose of 300 mg. of dicumarol should be given. Each morning thereafter a prothrombin test should be performed. If the control time is 15 seconds, as it is in the author's laboratory, the following schedule can be used. Until the prothrombin time reaches 30 seconds, from 100 mg. to 200 mg. of dicumarol should be given *after the prothrombin time for that day is known.* When the level of 30 seconds is reached, the dosage should be reduced to 100 or 50 mg. daily until a level of 35 seconds is obtained. After this level is reached, no further dicumarol should be given until the level descends to approximately 30 seconds or lower. The purpose of this procedure is to keep the prothrombin time between 25 and 40 seconds if possible, on the basis of a control prothrombin time of approximately 15 seconds. The ideal prothrombin time during adequate therapy is between two and two and one-half times the control if this be below 20 seconds.* If the prothrombin time reaches 50 seconds, the patient should be observed carefully for evidence of bleeding. If this occurs, or if the prothrombin time reaches 60 seconds, a dose of vitamin K (Hykinone, Synkovite, or menadione bisulfite) of 64 to 72 mg. should be given intravenously, and this should be followed by a similar dose in another four hours. On the following day, the prothrombin time should again be determined. It will usually be lower. If this is not the case, further dosages of vitamin K may be given. In the event of bleeding of any marked degree, or if the prothrombin time reaches 100 seconds or more, this treatment should be supplemented by transfusions of *fresh whole blood.* Banked blood of more than 1 or 2 day's age is definitely less satisfactory. Using the technic outlined above, we have very rarely had need for transfusions during the last several years nor, since 1941 when the author began the use of anticoagulants (and this experience has involved their use in several thou-

* This formula was first suggested by E. Sterling Nichol.

sand cases), has death from their use occurred on his service.

This experience is cited to indicate that if anticoagulant therapy is employed with proper care the risks are not excessive. They have been grossly exaggerated as a result of poorly controlled therapy, or by the use of these drugs in the face of definite contraindications which may or may not have been recognized.

3. *Contraindications.* Under the following circumstances, anticoagulants must be used cautiously or not at all:

a. Prothrombin deficiency (hypoprothrombinemia or potential prothrombin deficiency).
   (1) Vitamin K deficiency.
   (2) Severe hepatic disease.
b. Vitamin C deficiency.
c. Renal insufficiency.
d. Blood dyscrasias with impairment of the mechanism of hemostasis.
e. Interruptions of the continuity of the vascular system; for example, by surgical operation:
   (1) Recent operations on the brain or spinal cord.
   (2) Recent surgical operations leaving raw surfaces.
   (3) Postoperative tube drainage of wounds of viscera.
   (4) Operations performed in the presence of obstructive jaundice, external biliary fistula, or severe liver damage.
f. Late pregnancy.
g. Subacute bacterial endocarditis.

Summary

Coronary thrombosis with myocardial infarction is one of the most serious diseases which is frequent in the population over the age of 40. Until recently, treatment consisted of measures including rest and sedation which have the unfortunate effect of encouraging thrombosis. While these and other measures outlined in this paper have aided in the comfort of the patients and are believed to have influenced the course of the disease favorably, their usefulness has never been conclusively established. Clinical experience has nevertheless led to their acceptance, and they are recommended in the light of our present knowledge.

The anticoagulants, dicumarol and heparin, were first used experimentally and, thereafter, clinical experience seemed to justify their more general acceptance in practice. In the case of these drugs, however, another step of importance was taken. The Committee on the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction studied 1,031 cases under a statistically valid program. Approximately one-half of these received the best available type of treatment used prior to anticoagulant therapy; the other half received anticoagulant therapy in addition. The results were strongly in favor of the use of anticoagulants in the sense that both the death rate and the incidence of complications were decreased. A brief summary of these findings has been presented above. On the basis of this study the more general use of anticoagulants in the treatment of this serious disease is recommended. It is also suggested that other drugs be subjected to similarly controlled studies before they are accepted by the medical profession as being of established value.

Addendum

Since this paper was prepared, Tromexan, another coumarin, has become available. It acts more quickly than dicumarol (18 to 24 hours) and does not have so lasting an effect. The dosage is five or six times that required for dicumarol, and administration of the drug must be controlled by the prothrombin time determination. Further reports evaluating Tromexan will appear within the next few months.

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ABSTRACTS

Editor: SAMUEL BELLET, M.D.

BACTERIAL ENDOCARDITIS

Orgain, E. S., and Donegan, C. K.: The Treatment of Bacterial Endocarditis. Ann. Int. Med. **32:** 1099 (June), 1950.

This report represents the total experience of the Duke Hospital in the treatment by various methods of 38 instances of bacterial endocarditis. During the presulfonamide period (1930 to 1937), when therapy was nonspecific and unsatisfactory, 41 instances of bacterial endocarditis were observed. Of these, 1 patient survived following the use of autogenous vaccine therapy. In the sulfonamide period (1938 to 1943), the diagnosis of bacterial endocarditis was made in 51 instances. Treatment with one or more of the sulfonamides was administered to 41 patients. Four patients survived, a recovery rate of 10 per cent. Of 24 patients who received the sulfonamides, 2 were cured (8.3 per cent); of 17 patients who received the combination of sulfonamide and fever therapy, 2 were cured (11.8 per cent). During the peridd of penicillin therapy (1944 to 1947), 44 patients were observed. Of 37 patients who received penicillin, 20 patients were cured (54 per cent). Adequate daily dosage of penicillin is of paramount importance, and depends to a large extent upon the sensitivity of the organism which may be determined by preliminary in vitro studies. If the organism proves sensitive, therapy should begin at not less than 500,000 units of penicillin per day, and, if resistant, at not less than 1,000,000 units per day. The various technics of administration have not demonstrated any individual superiority. Anticoagulant therapy has not altered the final therapeutic results and is potentially dangerous. The treatment should last at least four to six weeks initially and longer if a relapse occurs.

WENDKOS

BLOOD COAGULATION

Olwin, J. H.: The Significance of Different Methods for Prothrombin Estimation and Their Relative Values. Surg., Gynec., & Obst. **90:** 423 (April), 1950.

It has been shown that in the one stage method of determining the prothrombin level in the blood, the end point in the test may be reached when as little as 40 per cent of the available prothrombin has been converted to thrombin. In other words, a plasma containing 40 per cent of the normal amount of prothrombin might give a 100 per cent prothrombin estimate by this method. Furthermore, in carrying out the test, such factors as fibrinogen, prothrombin accelerator, and the various anticoagulation substances are uncontrolled. The two stage method, which allows the prothrombin conversion to go to completion, and then in a second step permits the thrombin thus formed to act on a standardized fibrinogen solution, eliminates a number of the variables present in the one stage test. The chief objection to it is that it is difficult to perform.

The two stage test is a more accurate measure of available prothrombin, while the one stage test gives more information regarding the likelihood of bleeding, since it is a measure of the activity of a number of factors, both coagulation and anticoagulation. As an estimate of liver function, both methods are of value, although the two stage test, being a more sensitive reflection of changes in prothrombin, may show degrees of liver damage not registered by the one stage test.

With regard to the control of anticoagulant therapy, the one stage method is a more sensitive measure of heparin effect than the more commonly used coagulation time of whole blood. In dicumarol therapy, efforts are directed toward the control of the single factor, prothrombin, and the two stage method is preferable. However, the one stage test is of value as a measure of the overall safety factor.

ABRAMSON

Bauer, G.: Nine Years' Experience with Heparin in Acute Venous Thrombosis. Angiology **1:** 161 (April), 1950.

The author reviews the results of the use of heparin in the routine management of thromboembolic disease during a nine year period (1940–1949) at the Mariestad Hospital, Sweden. Management consisted of (1) very early diagnosis of incipient thrombosis, (2) energetic treatment with heparin by intermittent intravenous injection, and (3) early mobilization of the patient. Clotting times were not determined routinely. Four hundred and forty cases of thromboembolism were diagnosed and 438 were recognized early enough to be treated with heparin. There were only 2 deaths. Complications occurred in less than 4 per cent of the cases and included nonfatal pulmonary embolism, recurrence, slight hemorrhagic

tendency, and anaphylaxis. Thirty-nine patients had pulmonary embolism before undergoing treatment and all recovered.

WESSLER

Freeman, N. E., Wylie, E. J., and Gilfillan, R. S.: Regional Heparinization in Vascular Surgery. Surg., Gynec., & Obst. **90**: 406 (April), 1950.

The authors used regional heparinization in patients following the removal of arterial emboli and after the repair of a traumatized artery and excision of an aneurysm. In some instances the intra-arterial injections were continued for several days postoperatively. In others the injection was made at the time when the operation was performed. It was concluded that regional heparinization is of value in the prevention of thrombosis at the suture line. Furthermore, this form of administration of an anticoagulant reduces the danger of hemorrhage from the wound.

ABRAMSON

Smith, G. V. S.: A Further Report on Dicumarol Prophylaxis against Venous Thrombosis in Women Undergoing Surgery. Surg., Gynec., & Obst. **90**: 439 (April), 1950.

The purpose of this study was to determine whether dicumarol, given in small doses so as to avoid hemorrhage as well as the necessity of extensive laboratory control, would have any demonstrable effect in reducing postoperative thromboembolic crises. The majority of the patients in the group were over 35 years of age and undergoing major pelvic and vaginal plastic surgery. Most of the subjects were given dicumarol one to two days postoperatively and again five days later. A third dose was prescribed after an additional five days if the patient was still in bed. Prothrombin determinations demonstrated that in most women the doses of 100 to 200 mg. were sufficient to prolong the time appreciably by the second day after ingestion, this effect usually lasting two to five days. Comparison between the dicumarol-treated group and similar untreated groups gave fair but not striking evidence supported by statistical analysis that the drug reduced thromboembolic complications, but only during the period of its action.

ABRAMSON

Goldfeder, A., Bloom, D., and Weiner, M.: A New Improved Method for Determination of Prothrombin Levels in Blood. Science **111**: 365 (April), 1950.

The authors describe a simple, reproducible and economical method for determining prothrombin levels in blood. The procedure consists of drawing whole blood into capillary tubes containing dry oxalate, adding this to a measured amount of thromboplastin on a slide, drawing the mixture in and out of the capillary tube, and timing the formation of a fibrin strand. The test can be performed with small volumes of blood, facilitating repeated determinations in small animals. In man, it permits the bedside determination of prothrombin time from blood obtained by finger puncture.

SACHS

Jaques, L. B., Gordon, E., and Lepp, E.: A New Prothrombopenic Drug, Phenylindanedione. Canad. M. A. J. **62**: 465 (May), 1950.

The effect of 2-phenylindanedione-1,3, a drug resembling dicumarol in structure, was studied in animals. This compound reduced prothrombin time, but unlike dicumarol it permitted the prothrombin time to return to normal more quickly (within 36 hours). Single doses produced only a slight effect; on repeated administration it was as effective as dicumarol. One mg. per Kg. of body weight every eight hours increased prothrombin time to twice normal. However, vitamin K had no effect on the prolonged prothrombin time. Toxicity resembled that of dicumarol, but was rapidly reversed after withdrawal of the drug. No gross toxic effects were noted in dogs after the administration of 8.3 mg. per Kg. every eight hours for 48 days. The authors feel that the drug is highly effective in multiple doses and deserves further trial.

WAIFE

Blaustein, A.: A New Prothrombopenic Agent. Canad. M. A. J. **62**: 470 (May), 1950.

The disadvantages of dicumarol are the numerous side effects and the time required to develop therapeutic prothrombopenia. The author reports his clinical observations on 20 patients, 16 of whom had coronary heart disease or thrombophlebitis, who received a dicumarol-like substance, phenylindanedione. It was found that on an initial dose of 150 mg. divided into two or three doses a day the prothrombin concentration was reduced to about 25 per cent in 24 hours. Larger doses led to a greater reduction in prothrombin concentration. Like dicumarol some cases need more than others for similar effects. In this series about 50 mg. a day as maintenance dose kept the prothrombin concentration between 25 per cent and 30 per cent. No evidence of toxic effects on the liver or blood cells was found. Phenylindanedione appears to be safe and acts in half the time required by dicumarol.

WAIFE

CONGENITAL ANOMALIES

Chapman, C. B., and Gibbon, T. B.: New Aids in the Diagnosis of Dextrocardia. Am. Heart J. **39**: 507 (April), 1950.

The authors discuss the use of new diagnostic technics in the diagnosis of dextrocardia. By means of standard diagnostic methods, roentgenkymography, catheterization of the right side of the heart, and "unipolar" electrocardiography, the position of

the heart and its chambers was studied in 2 cases. One case, a 27 year old man, showed mirror-image dextrocardia associated with situs inversus, sinusitis, and bronchiectasis (Kartagener's triad). The other case, a 21 year old male student, had uncomplicated congenital isolated dextrocardia.

HELLERSTEIN

Adams, F. H., and Hansen, D. M.: Carbonic Anhydrase in Congenital Heart Disease. Proc. Soc. Exper. Biol. & Med. **73**: 642 (April), 1950.

Children with cyanotic congenital heart disease frequently tolerate relatively low degrees of oxygen saturation of the blood without any noticeable effects on the intelligence or on the state of consciousness when at rest. An investigation was made of the possible role of carbonic anhydrase in the blood of children with cyanotic congenital heart disease. Carbonic anhydrase is an enzyme, present in the hemoglobin of red cells, which accelerates the reaction of carbonic acid to carbon dioxide and water.

The carbonic anhydrase level in the blood was determined in 18 patients of different ages with proved congenital heart disease of the cyanotic type. The values found were compared with those obtained on 6 patients with congenital heart disease of the acyanotic type, 13 normal newborn infants and 27 patients with no cardiac disease who varied in age from 1 week to 20 years. The carbonic anhydrase was elevated in all of the patients with cyanotic congenital heart disease as compared with patients with acyanotic congenital heart disease or with no heart disease. When the results were corrected for the increased hematocrit, the blood carbonic anhydrase of the cyanotic patients did not differ significantly from that of the acyanotic patients of similar ages.

MINTZ

Wilson, J. G., and Warkany, J.: Cardiac and Aortic Arch Anomalies in the Offspring of Vitamin A Deficient Rats Correlated with Similar Human Anomalies. Pediatrics **5**: 708 (April), 1950.

After weaning, 400 female rats were placed on vitamin A deficient diets containing only sufficient carotene to permit continued growth. On attaining sexual maturity, the carotene was eliminated from their diets. They were mated with male rats who had been fed adequate diets. Of a total of 1168 offspring, 75 per cent possessed some developmental defect of the eyes. No instance of another anomaly occurring in the absence of ocular manifestations has ever been found in rats with maternal vitamin A deficiency.

Using the ocular manifestations as a criterion of maternal vitamin A deficiency, the hearts and major thoracic vessels of 64 newborns and fetuses of 17 days gestational age and over, were studied. Nineteen offspring of comparable age from adequately fed mothers were used as controls. Twenty-eight of the 64 young studied showed congenital abnormalities. Interventricular septal defects were found in 22 with the majority of the defects occurring at the base of the septum. Sixteen of these had other cardiovascular abnormalities. Aorticopulmonary septal defects were observed in 3 cases. Embryologic aortic arch anomalies occurred in 22 cases, of which 16 were associated with an interventricular septal defect. These abnormalities included a retrograde subclavian artery, a right-sided aortic arch with 5 variants, the absence and other variations of the ductus arteriosus, the absence of the aortic arch and agenesis of the left pulmonary artery.

The authors state that many of the cardiovascular anomalies observed in these rats closely simulated malformations observed in man. They further emphasize that environmental as well as genetic factors may alter the development of the cardiovascular system.

MARGOLIES

Adams, F. H., LaBree, J. W., and Stauffer, H. M.: Right Heart Catheterization in Acyanotic Congenital Heart Disease. Journal-Lancet **70**: 159 (May), 1950.

Forty patients with acyanotic congenital heart disease, who had presented diagnostic problems, were studied. The over-all findings suggested that the clinical diagnosis and x-ray diagnosis were reliable in approximately one half of the cases only. The clinical diagnosis appeared to be more reliable in patients with patent ductus arteriosus while the x-ray diagnosis was more reliable in patients with interatrial septal defects. The real value of heart catheterization, therefore, is in that group of patients whose disease presents unusual features.

WAIFE

Norman, J. A., Schmidt, K. W., and Grow, J. B.: Congenital Arteriovenous Fistula of the Cervical Vertebral Vessels with Heart Failure in an Infant. J. Pediat. **36**: 598 (May), 1950.

The authors describe the case of a 6 months old white infant, born at term with no history of trauma to the neck region, who entered the hospital with a temperature elevation and a cough which was proved to be pertussis. By the third day definite signs of congestive failure were apparent. In the left posterior triangle of the neck, there was discovered a palpable thrill and a loud continuous bruit with systolic accentuation. This was transmitted to the crown of the head, the base of the neck, and the left elbow. By digital compression at the point of maximum bruit, an immediate decrease in heart rate of 25 beats per minute, and a rise in blood pressure in the right arm from 88/26 to 106/54 (Branham's bradycardia) was produced. Because of these findings, a diagnosis of arteriovenous fistula of one of the major vessels of the left cervical region with associated heart failure was made.

At operation, the fistula was found overlying the transverse process of the second cervical vertebra and was removed; it measured 8 mm. in diameter The vertebral artery and vein were the chief vessels involved. The bruit and thrill disappeared and the pulse rate was below 100 by the third postoperative day. The chest film taken seven days after operation showed a striking decrease in the transverse diameter of the heart and clearing of the pulmonary congestion. Nine months later, the child was still in good health.

The authors could find no other case of congenital arteriovenous aneurysm of the vertebral vessels in the medical literature.

MARGOLIES

Freeman, N. E., Miller, E. R., Stephens, H. B., and Olney, M.: Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions. II. Coarctation of the Aorta. Ann. Int. Med. **32**: 827 (May), 1950.

Because intravenous angiocardiography in cases of coarctation of the aorta has not been able to demonstrate the stenotic segment entirely satisfactorily, retrograde arteriography was used in 15 patients in whom the diagnosis of coarctation of the aorta had been made on the basis of the clinical findings. The ages ranged from one year to 35 years. The injection was made into the left common carotid artery in all cases, after the vessel had been exposed under local anesthesia. Seventy per cent Diodrast was found to give the most satisfactory result. The dose found to be most satisfactory was approximately 1 cc. per Kg. of body weight up to a maximum of 50 cc. For satisfactory visualization, it is imperative that the first film of the series be taken immediately on completion of the injection and the remaining 2 to 3 films should be exposed as rapidly as the cassettes can be changed by hand. In one patient, a hematoma developed in the wound. Since care was taken to avoid entrance of the dye into the cerebral circulation, there were no other complications. In 9 of the patients, the exact location, degree, and extent of the stenosis were visualized, and these findings were confirmed at operation. Unnecessary thoracotomy was avoided in 4 of the patients because the nature of the aortic defect visualized by this means indicated that operation had little to offer in these particular instances.

WENDKOS

Dutra, F. R.: Anomalies of Coronary Arteries. Arch. Int. Med. **85**: 965 (June), 1950.

Two anomalies of the coronary arteries are reported. In an infant whose left coronary artery arose from the right pulmonary artery, the supply of oxygen to the myocardium of the left ventricle was insufficient to maintain the integrity of the tissues. In spite of the fact that the anoxia was of such a degree as to result in focal necrosis and fibrosis of the myocardium, there was no apparent tendency toward extension of branches from the right coronary artery into the wall of the left ventricle to compensate for this deficiency of oxygen. On the other hand, in the second case a complete absence of the left coronary artery was accompanied by the development of supplementary branches from the right coronary artery to the left side of the heart, and there was no apparent functional or anatomic abnormality of the myocardium.

It is suggested that the development of supplementary (collateral) circulation in the myocardium is not stimulated by local anoxia, but that pressure gradients may play a significant role in this phenomenon.

BERNSTEIN

CONGESTIVE HEART FAILURE

Branwood, A. W.: Some Observations on Liver Function in Heart Failure. Edinburgh M. J. **57**: 129 (March), 1950.

The author reviewed the clinical features of a group of patients with congestive heart failure to evaluate the part played by venous congestion of the liver in their symptoms. In 456 cases of congestive failure the liver was found to be enlarged in every case by the percussion method. In 44 per cent of these, enlargement was rather sudden. Following recovery from congestive failure the liver remained enlarged in 22.5 per cent and it was tender in about half of these. Jaundice was present in 18 per cent. One hundred twenty-six out of 456 cases had clinical jaundice, and of these 81 died, a 64 per cent mortality. This suggests that jaundice indicates a poor prognosis.

Seventy-eight per cent of these cases had ascites. In 5, ascites was the first sign of congestive failure, although all 5 were chronic alcoholics with evidence of concomitant portal cirrhosis. Urobilinogen was present in excess in the urine of 20 patients. It persisted in 4 who had apparently recovered although the liver remained palpable in 2 of these. If previous liver disease can be excluded the persistence of excess urobilinogen in the urine suggests a poor prognosis. The cephalin flocculation test was positive in 20 cases.

Many factors influence the liver function tests; these include circulatory disturbances, hepatocellular damage, conditioned nutritional deficiency, fever and bed rest. The author feels that cardiac cirrhosis or the hepatic fibrosis of heart disease cannot be diagnosed with certainty. It should be suspected in patients who have recurrent bouts of cardiac failure especially in the presence of rheumatic heart disease, and who complain of vague symptoms of indigestion, flatulence, right upper quadrant pain with or without hepato- or splenomegaly.

WAIFE

Richdorf, L. F.: Myocardial Failure in Children with Brain Involvement. Journal-Lancet **70**: 166 (May), 1950.

The author presents the case reports of 2 children who presented at necropsy both cardiac and neurologic findings. A 5 year old boy ran a slow course of progressive congestive failure. Autopsy revealed a heart weighing 330 Gm., lymphocytic and fibroblastic infiltrations, absent Aschoff nodules and normal valves. Subacute encephalitis was present. No etiologic agent was discovered. The second child was a 7 year old boy with congestive failure. Hemiplegia was caused by occlusion of the left middle cerebral artery. The heart was enlarged and showed thrombi in the left auricular appendage, but there was no microscopic evidence of myocardial involvement. No etiologic diagnosis could be made. Both children had chickenpox before the onset of their illnesses.

WAIFE

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Latscha, B., Lenègre, J., and Mathivat, A.: A Case of Embolism of a Coronary Vessel and a Case of Occlusion of a Coronary Ostium during the Course of Bacterial Endocarditis. Arch. d. mal. du coeur **42**: 729 (July), 1949.

Occlusion of a coronary vessel in the course of subacute bacterial endocarditis is a rare occurrence. The authors collected 13 cases from the literature and they reported two of their own. The first was a 31 year old woman with a typical subacute bacterial endocarditis superimposed on an old rheumatic mitral and aortic lesion. After one month of successful penicillin therapy the patient suddenly developed severe anginal pain with electrocardiographic signs of an anterior wall infarct. She died in progressive heart failure 48 hours later. The autopsy revealed a clot thought to be an embolus in an otherwise normal anterior descending branch of the left coronary and a macroscopically visible infarct of the anteroseptal and apical region of the left ventricle. The second observed case was that of a 39 year old man with seropositive aortic insufficiency who died suddenly in the course of progressive heart failure which had not responded to treatment. At post mortem, an endocarditis of both mitral and aortic valves was found. A large polypous vegetation on the right aortic leaflet completely occluded the ostium of the right coronary. No myocardial infarction was present in this case.

The authors conclude that the usual outcome of a coronary occlusion in the course of a subacute bacterial endocarditis is sudden death. The development of myocardial infarction is a rare event and seen only in cases who survive 24 to 36 hours.

PICK

Clagett, A. H., Jr., Benge, J. H., and Hooker, J. W.: Rupture of the Heart following Myocardial Infarction: Data from a Small Hospital. Am. J. M. Sc. **219**: 513 (May), 1950.

A series of 7 cases of myocardial rupture is reported because they occurred in a small hospital during a single year. Myocardial rupture is most likely to occur during the first two weeks following an acute infarct. Keeping the patient at absolute bed rest during this period will minimize the danger of this complication. The data presented, together with those of Foord, suggest that the use of anticoagulant drugs does not predispose to myocardial rupture, but statistical analysis of a much larger series of cases is necessary.

DURANT

Gillick, F. G., and Schneider, J.: Abnormal Electrokymograms from the Wall of the Ventricle with and without Evidence of Myocardial Infarction. Am. J. M. Sc. **219**: 500 (May), 1950.

The authors present the electrokymographic observations of left ventricular motion in 48 patients having precordial distress, as well as the clinical diagnoses of a group of 18 patients who had abnormal electrokymograms of the right ventricle. Abnormal tracings from the wall of the left ventricle were observed in myocardial infarction, coronary insufficiency, angina pectoris, and in patients with symptoms atypical of angina pectoris. Such abnormal findings may be obtained in the presence of normal or borderline routine electrocardiograms. On the other hand, normal electrokymograms can be obtained in the positions studied from the left ventricle of patients with myocardial infarction, angina pectoris, and coronary insufficiency. Abnormal electrokymograms can be obtained from the wall of the right ventricle, and 15 of 18 patients with this finding had evidence of cardiac or pulmonary disease or both. Abnormal electrokymograms can be obtained from the wall of both ventricles in the same individual.

An explanation is offered for the abnormal electrokymogram findings: the myocardium of the ventricular wall is unable to overcome the load placed upon it as effectively as a normal myocardium, due to some deficiency in its elastic and/or contractile properties. And further, the burden for the cardiac output may then principally rest on the piston-like action of the interventricular and auriculoventricular septa with the walls acting as passive retainers to a greater or lesser extent.

DURANT

Moran, T. J.: Autopsy Incidence of Pulmonary Embolism in Coronary Heart Disease. Ann. Int. Med. **32**: 949 (May), 1950.

In analyzing 635 consecutive autopsy protocols in an institution where the average age at autopsy was 60.04 years, the author found that in 88 cases

death was due to some form of coronary heart disease. Pulmonary embolism occurred in 26 of these 88 cases of coronary heart disease. Massive embolism occurred 8 times whereas minor pulmonary emboli were present in 18 cases. The incidence of pulmonary embolism was the same regardless of whether or not myocardial infarction had occurred but the incidence of massive embolism was higher in the group not showing myocardial infarction. The contributory role of the minor pulmonary emboli is difficult to evaluate, but the occurrence of 11 lung infarcts in the cases of minor embolism indicates that they had a bearing on the fatal outcome in at least some of the deaths. The presence of clinically diagnosed congestive heart failure did not appear to affect the incidence of pulmonary embolism in the coronary heart disease group for, of the 26 cases of pulmonary embolism in this group, 13 developed in patients showing clinical congestive failure and 12 developed in patients with no clinical congestive failure. However, evidence of some degree of congestive heart failure was found at autopsy in most of these 12 subjects.

WENDKOS

Fox, P. F., Cirrincione, F. A., and Johnson, H. S.: Coexistent Acute Myocardial Infarction and Acute Appendicitis with Perforation. Surgery **27**: 780 (May), 1950.

This is a case report of an acute anterior wall myocardial infarction complicated on the sixth day by acute suppurative appendicitis with rupture and generalized peritonitis. The heavy sedation required to relieve the cardiac pain probably masked the pain of the appendicitis. The high mortality in surgical intervention during the acute phase of coronary occlusion is stressed. The authors feel that in such cases ether is the anesthetic agent of choice.

KLOSK

Doscher, N., and Poindexter, C. A.: Myocardial Infarction without Anticoagulant Therapy. Am. J. Med. **8**: 623 (May), 1950.

The authors analyzed 414 consecutive cases of myocardial infarction not treated with anticoagulants between 1935 to 1948. It was found that age, sex, pre-existing hypertension, the presence of angina or previous infarction materially affect the statistical deductions of previous reports. The use of average ages, for example, is misleading since significantly different age-distribution curves may give identical figures for average age. A difference in mortality rate may result as a reflection of the masked age distribution rather than as the result of therapy. Since the mortality rate from myocardial infarction is about 50 per cent higher in women than men, the sex distribution in a series will influence the mortality rate. The alternate case method of study does not equalize these variables.

In this series 15.5 per cent of the patients died, and 6.5 per cent had one or more thromboembolic phenomena. The combined mortality rate of over 4000 cases in the literature was 23.5 per cent, and embolic phenomena occurred in 10.8 per cent of 1927 cases.

WAIFE

ELECTROCARDIOGRAPHY

Epstein, N., and Gardam, J. D.: A Study of the Q-T_c Interval in the Electrocardiogram of Rheumatic Fever. J. Pediat. **36**: 583 (May), 1950.

Three hundred and twenty-five electrocardiograms taken on 29 male and 26 female children with active carditis or inactive rheumatic heart disease were analyzed. There were 229 tracings taken on children during the active phase of the disease, and 96 during the inactive period. A Q-T_c interval of 0.41 second or more was considered abnormal.

The corrected Q-T interval was 0.41 second or more in 38 per cent of the electrocardiograms of patients with active carditis, whereas only 27 per cent of the electrocardiograms taken during the inactive phase of the disease had a prolonged Q-T_c interval. In the same patients, the highest Q-T_c interval during the active phase of the disease was compared with the highest Q-T_c interval during the inactive phase. The interval was prolonged in 47 per cent during the active episodes, and in 29 per cent in the quiescent period. Electrocardiographic abnormalities other than Q-T_c interval prolongation were found in 54 per cent of the serial tracings during active episodes. The P-R interval was prolonged in 30 per cent of these. The duration of the Q-T_c interval was definitely not prolonged in all cases of rheumatic carditis. However, it was prolonged in 76 per cent of the patients with pancarditis and congestive failure. Fifty per cent of the patients in the quiescent period who had cardiac hypertrophy had an increased Q-T_c interval. The incidence of Q-T_c interval prolongation found was no greater than the accepted incidence of electrocardiogram abnormalities in active carditis.

The authors conclude that Q-T_c intervals in electrocardiograms, per se, are not diagnostic of active rheumatic carditis.

MARGOLIES

Master, A. M.: The Two-Step Exercise Electrocardiogram: A Test for Coronary Insufficiency Ann. Int. Med. **32**: 842 (May), 1950.

Electrocardiographic indications of coronary insufficiency are more likely to become evident in tracings made following exercise than in those made when the patient is resting. To reveal such changes, electrocardiograms have been made after the two-step exercise test. In interpreting the electrocardiogram following such exercise, the P-R interval is taken as the control level. Depression of the S-T segment of over 0.5 mm. in any lead is considered a positive result. Such a change is usually maximal

in the precordial lead. Other changes considered to be corroborative of coronary artery disease are a change from an upright T-wave to an isoelectric or inverted T-wave, a change from a flat or negative to a positive T-wave, premature beats or a more significant arrhythmia, widening of the QRS complex, intraventricular or bundle branch block, large Q waves, prolongation of the P-R interval or heart block.

The value of this added refinement in the study of patients who experience recurrent bouts of pain in the chest is illustrated in 3 cases.

WENDKOS

Mahaim, I., and Rossier, P. H.: Acute Myelogenous Leukemia, Hemorrhagic Diathesis, and A-V Block with Lesions in the Specific Tissue. Cardiologia **15**: 196, 1950.

A 37 year old woman developed fever and headaches. An acute leukemia with paramyeloblasts was found. The first electrocardiogram was normal; another tracing obtained 17 days later showed complete A-V block with bradycardia. Autopsy confirmed the clinical diagnosis. Extensive leukemic infiltrations were found in the upper interventricular septum, particularly in the fibrotic part. The A-V node was partially destroyed.

SCHERF

Odle, S. G., Wechsler, L., and Silverberg, J. H.: The Electrocardiographic Diagnosis of Coronary Insufficiency by Leads Demonstrating the Left Ventricular Cavity. Am. Heart J. **39**: 532 (April), 1950.

The authors indicate that electrocardiograms obtained with the exploring electrode in the left supraclavicular fossa or over the left clavicle at the lateral border of the sternocleidomastoid muscle reflect the potentials of the left ventricular cavity. In 69 of 100 patients, such tracings were of the QS–inverted T pattern. The authors believe that these leads explore the subendocardial surface of the left ventricle and demonstrate changes indicative of subendocardial damage where standard methods are unsuccessful.

HELLERSTEIN

Schwedel, J. B., Samet, P., and Mednick, H.: Electrokymographic Studies of the Relationship between Electrical and Mechanical Events of the Cardiac Cycle. Proc. Soc. Exper. Biol. & Med. **73**: 591 (April), 1950.

This study was performed because of the difference of opinion as to whether or not there is a correlation between electrical and mechanical events of the cardiac cycle. Simultaneous electrokymograms of the pulmonary artery and ascending aorta and electrocardiograms were done. In a study of more than 50 normal subjects, the pulmonary artery ejection phase at times preceded aortic ejection (as measured by the upstroke of the electrokymographic curves in both instances) by as much as 0.03 second or followed it by as much as 0.02 second. Of 25 cases of bundle branch block, the authors found correlation between the electrical and mechanical events in only 8. In 17 cases the relation between the onset of the pulmonary artery upstroke and that of the ascending aorta was within the normal range. Repetition of the curves at different times gave the same results within the error of measurement of 0.01 second. These results indicate a lack of correlation between electrical and mechanical events of the cardiac cycle.

MINTZ

Bellet, S., Steiger, W. A., Nadler, C. S., and Gazes, P. C.: Electrocardiographic Patterns in Hypopotassemia: Observations on 79 Patients. Am. J. M. Sc. **219**: 542 (May), 1950.

The importance of the subject of hypopotassemia is stressed because of the frequency with which it occurs and the profound nature of the disturbances of body function that exist during this state. Emphasis is placed upon the value of electrocardiography as an aid in diagnosis and as a means of following the effects of therapy.

The electrocardiographic patterns observed in 79 patients with hypopotassemia of various etiologies are presented. Five different patterns of T wave and S-T segment changes accompanied by Q-T segment prolongation were observed. These consisted of (1) depression of the S-T segment of varying degrees, (2) inversion of T waves, (3) T waves of normal amplitude with prolongation of the Q-T interval, (4) low amplitude of T wave, and (5) prominent U wave following T wave. The first two patterns constituted the changes shown by 80 per cent of those observed. Pattern 1 was observed most frequently after prolonged vomiting and pattern 2, in diabetic acidosis. The changes observed were immediately reversible following the administration of potassium. It was found that the U wave is an important criterion of hypopotassemia, having been present in 33 cases (42 per cent). Evidence is presented which suggests that lengthening of the Q-T or Q-U interval are both important in the diagnosis of hypopotassemia.

In some instances of alkalosis a diminished serum or ionizable calcium probably contributed to the electrocardiographic changes. However, the effect of administration of this electrolyte suggested that its role in the production of the alterations was a minor one.

DURANT

HYPERTENSION

Bello, C. T., Moss, W. A., and Weiss, E.: Effect of Orally Administered Dihydroergocornine (D.H.O. 180) on Hypertension. Am. J. Med. **8**: 634 (May), 1950.

Dihydroergocornine (D.H.O. 180) is a derivative of the ergotoxine group of alkaloids with marked sympathicolytic and adrenolytic properties. Following a ten week control observation period the compound was administered orally in daily doses of from 4 mg. to 12 mg. to 10 hypertensive patients. After six weeks a placebo was substituted and maintained for four weeks. No significant hypotensive effect was demonstrated with this dosage which is 20 to 50 times greater than the effective intravenous dose. The subjects showed some lowering of blood pressure following intravenous D.H.O. 180.

WAIFE

Berthoud, E.: The Syndrome of Pseudotumor in Arterial Hypertension. Schweiz. med. Wchnschr. **80:** 548 (May), 1950.

The author studied 13 cases of hypertension with the symptomatology of a brain tumor. In 10 of the cases there were typical signs of increased intracranial pressure while in the remaining cases a tumor was suggested by epileptic attacks of the Jacksonian type. The arterial pressures varied between 220 and 330 systolic and 120 to 170 diastolic. In 10 cases left heart strain was found in the electrocardiogram. Heart failure was present only in one case. The death rate of patients with the first type of symptoms was 70 per cent in the first year. The 3 cases with epileptic attacks died within 2 to 5 years. The author concludes that both types represent a special form of the disease, which resembles malignant hypertension in course and prognosis.

PICK

Horne, S. F., Curtis, A. C., and Kahn, E. A.: Splanchnicectomy for Hypertension in Lupus Erythematosus and Periarteritis Nodosa. Ann. Int. Med. **32:** 1202 (June), 1950.

A 36 year old white man was subjected to splanchnicectomy because of a blood pressure which varied between 180/120 and 240/140 and an associated grade 4 retinopathy. Pre-operatively the renal function was excellent, although a slight degree of cylindruria and albuminuria was present; the electrocardiogram was normal; intravenous pyelogram was normal, and chest x-ray films disclosed a normal-sized heart. Seven years later he was entirely asymptomatic and his blood pressure was 132/80. In some of the tissue removed at operation there was one artery with a necrotic wall. Around the wall was a subacute periarteritis with many newly formed blood vessels. On the basis of this finding involving a single artery, a diagnosis of periarteritis nodosa was made. Hypertension in this case is considered to be related in some way to the vascular lesion. In contrast, a 42 year old woman with chronic lupus erythematosus involving the face, trunk, and hands who was subjected to the same operation for severe hypertension, died six months postoperatively although the hypertension was lowered to some degree by the splanchnicectomy.

WENDKOS

Leard, S. E., and Jaques, W. E.: Amyloid Disease with Hypertension. New England J. Med. **242:** 887 (June), 1950.

A case of hypertension secondary to amyloid contracted kidneys is reported. A 21 year old man was admitted to the hospital because of draining sinuses, one in the right knee of six years' duration, and one in the left hip of three years' duration. At this time hepatomegaly and splenomegaly were noted. He was treated with chemotherapy and during the next four years had four hospital admissions. During these admissions, beginning hypertension with eyeground changes and cardiac hypertrophy were noted. He was placed on a low protein–low salt diet and on veratrum viride. He reentered the hospital because of epistaxis and severe cramps in the legs, was found to be very anemic, and unable to eat. Despite intensive therapy, he died soon after admission.

Pathologic examination revealed amyloid deposition in all parts of the kidney, as well as in the arterioles of spleen, liver, gall bladder, stomach, pancreas, and periadrenal fat. The authors point out a correlation between nutrition and hypertension in cases of amyloidosis. They suggest that in young, well-nourished individuals, there is hypertension, whereas in cachectic patients, the blood pressure was low.

NADLER

Frant, R., and Groen, J.: Prognosis of Vascular Hypertension. Arch. Int. Med. **85:** 749 (May), 1950.

The authors report the results of a follow-up examination of 418 patients with hypertension (blood pressures above 155 systolic and 100 diastolic) who were reexamined after a period of eight to nine years. The death rate for men with essential hypertension exceeded the normally expected death rate for men in the same age groups by 102 per cent; for the women this figure was 91 per cent. Chronic nephritis increased the death rate in men by 587 per cent and in women by 150 per cent in excess of the normal. The total excess mortality for patients with hypertension of all types was 233 per cent for the men and 201 per cent for the women.

Analysis of the cases of essential hypertension showed that the mortality increased with increase of both systolic and diastolic blood pressure. However, the condition of the fundus of the eye is a better guide for the prognosis of hypertension than the increase in blood pressure. Heart disease, albuminuria and diabetes appeared to reduce the expectation of life, even more for women than for men. Hypertension accompanied by obesity appeared to be

prognostically more favorable than the same hypertension in patients whose weight was normal or low. Hypertension in young subjects carried a relatively shorter life expectancy than high blood pressure in old age. Among the causes of death of the patients with all forms of hypertension, heart disease (40.9 per cent) took the lead; next came carcinoma (16.4 per cent), followed by uremia (14.9 per cent) and apoplexy (8.6 per cent). Apoplexy as a cause of death was almost seven times as common among women (14.2 per cent) as among men (3.1 per cent). For 9.4 per cent of the deaths in this series the cause could not be ascertained.

BERNSTEIN

Fishback, D. B.: A New Test for Vasopressor Substances in Hypertension. Am. J. M. Sc. **219:** 517 (May), 1950.

A new test for vasopressor substances in the blood of hypertensive cases is presented. The test involves the injection of 3 cc. of human blood serum into the ear vein of a rabbit and the subsequent determination of the animal's circulation time by a fluorescein method. It was found that serum from hypertensive patients usually prolonged the circulation time (to more than 7.5 seconds). Serum from persons with normal blood pressure almost always yielded negative tests. It is assumed that the increased circulation time obtained with serum from hypertensives is due to the presence of excessive vasopressor substances. Further studies are indicated to further evaluate the test.

DURANT

Griffiths, A. L.: Hypertension of Renal Origin in Childhood. Arch. Dis. Childhood **25:** 81 (May), 1950.

The author describes 4 cases of severe hypertension in children which were presumably the result of renal lesions. In 3 of the cases the initial lesion was a pyelonephritis which became chronic and resulted in progressive renal damage with gross scarring. In 3 cases a unilateral nephrectomy was done; 1 patient was cured, a second presumably cured—the time was insufficient for proper evaluation—and a third, while not cured of the hypertension, was relieved of the symptoms of headache and frequent epistaxis. In the 2 successful cases, blood pressures dropped from 270/215 and 260/190, respectively, to within the normal range, and improvement in their general conditions was dramatic.

The author states that the absence of pus or albumin in the urine does not exclude renal disease, and that with a normal blood urea nitrogen level, severe unilateral renal disease can be present. An excretory pyelogram should be done on all children with hypertension. Since the complete absence of one kidney is not extremely rare, a retrograde pyelogram is necessary to differentiate between nonfunctioning kidney and complete absence of one kidney. Success in surgery is only anticipated when one of the kidneys is normal or only slightly damaged.

MARGOLIES

Spuehler, O.: The Differential Diagnosis of Hypertension from the Standpoint of Pathogenesis. Schweiz. med. Wchnschr. **80:** 538 (May), 1950.

Three main factors are essential in the pathogenesis of hypertension: a nervous, a renal, and a humoral one. Nervous impulses, originating in the pressoreceptors and in subthalamic centers, regulate tonus and reactivity of peripheral vessels. Organic lesions, such as sclerosis in the region of the carotid sinus, cerebral tumor or trauma, encephalitis or carbon monoxide intoxication, can produce persistent hypertension by disturbing the coordination of pressure-regulating nervous impulses. A primary renal pathogenic factor can be demonstrated in man in the presence of unilateral kidney disease when a drop in blood pressure occurs after nephrectomy. The humoral regulation of the blood pressure is dominated by the hypophysis, mainly through its adrenocorticotropic hormone (Addison's and Cushing's disease). Hypertrophy of the adrenal cortex is a common finding in hypertension. Climacteric hypertension can also be explained by an overfunction of the adrenal cortex following cessation of inhibitory effects of the ovaries on the hypophysis. Prolonged stress leads to stimulation of the adrenal cortex, which in turn stimulates the liver to excessive production of hypertensinogen. The use of a diet low in protein and salt, which lowers the blood pressure, is followed by a decrease in excretion of 17-ketosteroids in the urine.

PICK

PATHOLOGIC PHYSIOLOGY

Hemingway, A.: A Method of Chemical Analysis of Guinea Pig Lung for the Factors Involved in Pulmonary Edema. J. Lab. & Clin. Med. **35:** 817 (May), 1950.

A study of the various forms of pulmonary edema was made in order to produce a rational therapy based on pathogenesis. The methods for estimating the degree of pulmonary edema have been qualitative rather than quantitative. The method in use is to note the color and presence of hemorrhagic areas, to look for fluid, and to determine the consistency of the lung on palpation. These methods, while adequate for distinguishing between a normal lung and one that is grossly edematous, does not serve to distinguish mild edema; nor does it offer a quantitative evaluation of the degree of injury.

A method was devised to determine the quantities which change significantly during pulmonary edema. The quantities measured include lung weight, lung density, insoluble protein nitrogen of the lung,

pulmonary hemoglobin, and soluble (nonhemoglobin) protein nitrogen. These values were determined for the lungs of 10 normal guinea pigs.

MINTZ

Remington, J. W., Hamilton, W. F., Boyd, G. H. Jr., Hamilton, W. F., Jr., and Caddell, H. M.: Role of Vasconstriction in the Response of the Dog to Hemorrhage. Am. J. Physiol. **161:** 116 (April), 1950.

Hemorrhagic shock was induced and measured in anesthetized dogs by the methods outlined in the preceding article. Pressures and flow were altered by (a) Dibenamine and (b) extirpation of carotid sinus and/or epinephrine infusions. The dogs treated with large doses of Dibenamine (15 mg. per Kg.) had a more rapid fall in pressure and a greater decrease in cardiac output than did the controls. Peripheral resistance fell promptly, and lower terminal values were obtained. Fifty per cent of the Dibenamine-treated animals survived as compared with 8 per cent of the controls. The dogs treated with small doses of Dibenamine (5 mg. per Kg.) showed a survival rate of 72 per cent against 8 per cent for the controls, but there were no appreciable differences in the responses measured that would have explained the difference in the survival rate. Removal of carotid sinus, or epinephrine or Arterenol infusion induced prolonged episodes of vasoconstriction resulting in a rise in pressure and resistance, and a reduction in peripheral flow. Late in the course of hemorrhage, the values in these treated dogs differed but little from those of the controls.

The lethal bleeding volume of all controls varied, depending on the season, from an average of 30 ml. (summer) to 38 ml. (winter). Large doses of Dibenamine reduced the bleeding volume (21.2 cc.) per Kg.); Peripheral flow appeared adequate even at low pressures, so that the animals were able to walk about with pressures of less than 50 mm. Hg. The bleeding volume was slightly larger in the series subjected to epinephrine infusion, or carotid sinus section.

It is assumed that a central vasoconstrictor impulse controls peripheral flow through various organs, and may shunt blood to vital organs during hemorrhage. Local accumulation of metabolites during anoxia caused by the reduced flow through an organ convert the peripheral local vasoconstriction to local vasodilatation. If these local controls supervene, a general fall in peripheral resistance ensues with circulatory collapse leading to death. Dibenamine prevents local vasoconstriction and thereby tends to maintain adequate peripheral flow, even with low pressures. This may be the cause of the increased survival rate in Dibenamine-treated animals.

HECHT

Scherf, D., Morgenbesser, L. J., Nightingale, E. J., and Schaeffeler, K. T.: Further Studies on Mechanism of Auricular Fibrillation. Proc. Soc. Exper. Biol. & Med. **73:** 650 (April), 1950.

The authors studied the effect of cooling on auricular fibrillation produced by methods other than aconitine. Fibrillation was produced by three methods. One method employed faradization of the atria lasting 30 to 60 seconds. This type of fibrillation rarely persisted long enough for study. Auricular fibrillation was also produced by rapid stimulation with rhythmic electrical shocks. The most effective method for producing prolonged fibrillation was the application of a small strip of filter paper moistened with a concentrated solution of acetyl choline to the area of the sinus node.

Cooling of the sinus node and the atrial part of the A-V node was accomplished by the application of ice cold water in a glass tube or by direct application of ice cubes on these areas. The A-V node was cooled in three ways. One method was by pressure with the thermode against the outer lateral wall of the right atrium, towards the lower wall of the right atrial septum in the area of the A-V node. Another method was to lift the heart from its bed by elevation of the apex, and to cool the A-V node through the coronary sinus vein at its orifice in the right atrium. A third method was to clamp the superior and inferior vena cava and to open the atrium quickly and apply the thermode on the area of the atrial part of the A-V node near the orifice of the coronary sinus.

The results indicated that auricular fibrillation is not stopped by cooling the area of stimulation or by cooling the site of application of acetylcholine. In 24 of 27 experiments, however, the simultaneous cooling of the sinus and A-V nodes terminated the fibrillation. Interruption of the cooling caused the auricular fibrillation to reappear. These experiments tend to support the theory that in some forms of fibrillation more than one center of rapid stimulus formation is active. These experiments argue against the presence of a circus movement.

MINTZ

Waters, L. L., and deSuto-Nagy, G. I.: Lesions of the Coronary Arteries and Great Vessels of the Dog following Injection of Adrenalin. Their Prevention by Dibenamine. Science **111:** 634 (June), 1950.

Segmental necrosis of many of the small coronary arteries and arterioles, as well as extensive hemorrhages and necrosis of the pulmonary artery and aorta, developed in dogs given massive doses of adrenaline. Medial necrosis of the coronary arteries was frequently accompanied by periarteritic cellular inflammatory exudate or by perivascular fibrosis. Necrosis of the aortic adventitial vasa vasorum was prominent. The lesions reproduced the acute ar-

teriolar changes often encountered throughout the body in rapidly developing hypertension in man. Pretreatment with the adrenolytic substance Dibenamine prevented the development of these lesions. Dibenamine also abolished the rise in systemic pressure of subsequent adrenaline injections.

WAIFE

PATHOLOGY

Rosenberg, E. F., Bishop, L. F. Jr., Weintraub, H. J., and Hench, P. S.: Cardiac Lesions In Rheumatoid Arthritis. Arch. Int. Med. **85**: 763 (May), 1950.

Studies made at necropsy in the past five years have revealed that the incidence of rheumatic heart disease is far higher among patients who died with rheumatoid arthritis than it is in the general population. This observation has been out of line with the experiences of many clinicians who have examined the incidence of heart disease among living patients with rheumatoid arthritis.

One hundred and fourteen patients having rheumatoid arthritis of peripheral joints and 33 having rheumatoid spondylitis were examined in detail to determine the incidence of major and minor cardiac abnormalities. Similar studies were conducted concurrently on 100 nonarthritic persons, most of whom were well and a few of whom were undergoing treatment for injuries. Auscultatory, roentgenographic, sphygmomanometric and electrocardiographic studies of these two groups of subjects disclosed that the incidence of rheumatic heart disease in the arthritic groups, judged on clinical evidence, was not significantly higher than the incidence of this condition among the controls. No explanation for the apparent difference in the incidence of this complication in the living and the dead patients resulted from this study.

BERNSTEIN

McAllen, P. M.: Myxoma of the Left Auricle. Brit. M. J. No. 4659: 932 (April), 1950.

The author presents the findings in 3 fatal cases of myxoma of the left atrium, of which only one presented clinical manifestations of myocardial ischemia and dyspnea unrelated to posture. The remaining 2 cases had few symptoms of cardiac dysfunction. He feels that certain electrocardiographic changes may be expected in theory, such as exaggerated P waves and evidence of right ventricular strain, S-T depression and T wave inversion in Leads II and III. These findings may occur without any clear clinical explanation and are difficult to assess. Death may be due to hemorrhage into the tumor in some cases, while obstruction by the tumor may account for the remainder. It is concluded that the diagnosis is still an extremely difficult problem, but, with the aid of angiocardiography, confirmation is possible when tumor is suspected. Early recognition may ultimately lead to its surgical removal.

TANDOWSKY

Carter, M. G., and Korones, S. B.: Amebic Pericarditis, Review of the Literature and Report of a Case. New England J. Med. **242**: 390 (March), 1950.

The authors found 44 proved cases of suppurative amebic pericarditis reported in the literature. Of this group the diagnosis was established during life in 2 patients. The case reported in this article showed 2 liver abscesses; one in the left lobe communicated with the pericardial cavity. The diagnosis of pericarditis was made by electrocardiography. The ameba histolytica was found on pericardiotomy. The authors stress the importance of early diagnosis and therapy before liver abscesses rupture.

NADLER

PHARMACOLOGY

Walton, R. P., Leary, J. S., and Jones, H. P.: Comparative Increase in Ventricular Contractile Force Produced by Several Cardiac Glycosides. J. Pharmacol. & Exper. Therap. **98**: 346 (April), 1950.

Using both open-chest dogs with levers attached to the right ventricle and chronically operated animals in which strain gage equipment had been sutured to the ventricle and left in situ, the authors found that the intravenous administration of several digitalis glycosides produced significant increases in the force of contraction of the right ventricle; there were however no statistically significant differences among the glycosides in comparable dosage. The degree of increase in the contractile force measured was inversely proportional to the original isometric systolic tension. The time required for maximal increase in force of contraction varied among the glycosides employed. No electrocardiographic changes of significance occurred prior to the development of substantially increased force of contraction.

GROSSMAN

Gold, H., Cattell, McK., Modell, W., Greiner, T., and Guevara, R.: Local Emetic Activity of Glycosides of the Digitalis Series. J. Pharmacol. & Exper. Therap. **98**: 337 (April), 1950.

The existence of nausea and vomiting following oral administration of digitalis, long before obvious systemic action occurs, is strongly suggestive of local, as contrasted to central, emetic activity. The degree of local emetic activity of 4 glycosides—scilleroside, lanatoside C, scillaren A and ouabain—was studied in a group of cats given large, single oral doses and observed for retching and/or vomiting. Most potent was lanatoside C; intermediate

were scilleroside and scillaren; least apt to produce emesis was ouabain. In each case, emesis occurred after only a small fraction of the dose had been absorbed. Moreover, local emetic potency was not related to cardiac effects. It was observed too that the length of the interval prior to vomiting tended to vary inversely with the size of the dose.

GROSSMAN

Krayer, O.: Studies on Veratrum Alkaloids. XII. A Quantitative Comparison of the Anti-Accelerator Cardiac Action of Veratramine, Veratrosine, Jervine, and Pseudojervine. J. Pharmacol. & Exper. Therap. **98:** 427 (April), 1950.

Previously, secondary amine bases of steroid nature among the veratrum alkaloids had been found to antagonize the accelerator effect of epinephrine on the heart rate. This antiaccelerator property of the two glycosides, veratrosine and pseudojervine, and of their respective aglycones, veratramine and jervine, was measured with the use of heart-lung preparations receiving a constant rate of infusion of l-epinephrine. The use of these preparations permits more accurate standardization of effect. Veratramine was found to be fifty times as potent as jervine in its antiaccelerator effect; the glycosides, veratrosine and pseudojervine, had about the same degree of potency as their respective aglycones.

GROSSMAN

Thompson, W. S., Jr., McClure, W. W., and Landowne, M.: Prolonged Vasoconstriction Due to Ergotamine Tartrate. Arch. Int. Med. **85:** 691 (April), 1950.

A case is reported in which the chronic administration of ergotamine tartrate produced symptoms of vasoconstriction of five months' duration, with complete recovery following withdrawal of the drug and the intravenous injection of 140 mg. of sodium nicotinate. Data on biopsy of muscle, plethysmographic tests and values for skin temperature provided objective evidence of normal anatomic and physiologic vascular response despite the prolonged vasoconstriction. The administration of 10 mg. of Priscoline intravenously was ineffective in overcoming the vasoconstrictive effect of ergotamine. Sodium nicotinate proved to be an efficient vasodilator in the presence of vasoconstriction due to ergotamine. The absence of tissue necrosis and the demonstration of normal vessels at biopsy tended to support previous observations that intimal change is necessary in ergotism for stasis, thrombosis and tissue necrosis.

BERNSTEIN

Friedman, S. M., and Friedman, C. L.: A Screening Test to Indicate Opposition to the Cardiovascular-Renal Effects of Desoxycorticosterone Acetate in the Rat: The Effect of Adrenal Cortical Extract. Endocrinology **46:** 367 (April), 1950.

Using a dose of desoxycorticosterone acetate (DCA) just sufficient to cause a minimal elevation in blood pressure in rats along with a significant increase in heart weight and kidney weight, the authors investigated the inhibitory effect of many steroids on the hypertensive effects of DCA. Of the compounds tested, progesterone, testosterone, estradiol, pregnenolone, acetoxypregnenolone, "saturated 12-keto DCA," and hyaluronidase were all incapable of inhibiting the DCA effects studied. Large doses of lipo-adrenal cortex extract had an inhibitory effect on the cardiovascular-renal effects of DCA. The possibility is discussed that the adrenal gland might liberate some factor opposed to DCA.

CORTELL

Brown, R. V.: A Comparison of Several Dose-Action Curves for the Pressor Action of Epinephrine. J. Pharmacol. & Exper. Therap. **98:** 418 (April), 1950.

The dose-action curves of the pressor effect of epinephrine in 5 dogs were determined and an attempt made to fit to these data the curves previously obtained by other investigators. Using the method of least squares, the hyperbolic curve of Rosenblueth was the only one to exhibit good fit over the entire range measured. It is of interest that a hyperbolic curve of the same type $\left(y = \frac{x}{a + bx}\right)$ has been derived from hypotheses employed to develop the mechanism of chemical mediation of autonomic nervous system activity.

GROSSMAN

Burwell, W. B., and Hendrix, J. D.: Digitalis Poisoning. Am. J. Med. **8:** 640 (May), 1950.

The authors review the clinical and pharmacologic aspects of digitalis. The drug reduces heart size in both normal and diseased hearts; the cardiac output consequently varies, depending on the initial size of the heart. The refractory phase is prolonged and A-V conduction is slowed. Myocardial irritability increases.

The erroneous indications for digitalis include murmurs, routine preoperative preparations, angina pectoris, thyrotoxicosis and acute rheumatic fever. It is contraindicated in paroxysmal ventricular tachycardia and in certain cases of Adams-Stokes syndrome, intraventricular block and the Wolff-Parkinson-White syndrome.

Thirty-five cases of digitalis poisoning seen over a seven year period are described. Two of the 35 showed no clinical signs or symptoms suggestive of disease. In 10 cases no rational explanation for the use of digitalis could be found. In 26 cases the signs and symptoms of poisoning were ignored. The most common signs and symptoms were anorexia, nausea, vomiting and cardiac arrythmias. Among 25 instances of the latter premature ventricular beats

occurred in 20, 11 of which were characterized by bigeminy.

Electrocardiographic effects were sufficiently definite in 25 of 33 cases to be considered reasonably diagnostic. Digitalis preferably should be avoided prior to electrocardiographic study of suspected myocardial disease because digitalis T-wave changes may persist for several weeks after the drug has been discontinued.

In general the optimum dose is the minimum dose required to produce a desired effect. Ambulatory patients have a wider margin between therapeutic and toxic doses than have severe cases of heart failure. The degree of improvement with digitalis is of some prognostic value.

WAIFE

DiPalma, J. R., and Schultz, J. E.: Antifibrillatory Drugs. Medicine **29**: 123 (May), 1950.

The authors review the physiology of fibrillatory states, emphasizing the concept that fibrillatory agents act not by increasing irritability or excitability, but rather by depressant effects; the resulting areas of local block permit re-entry of impulses with culmination in fibrillation. This concept explains the paradoxical toxic effect of ventricular fibrillation which may occur with large doses of antifibrillatory drugs. The existence of conduction defects as a precursor of the fibrillatory state is also stressed.

It is shown that the most effective antifibrillatory drugs possess a roughly similar basic chemical structure, and that many of them have local anesthetic action. Among the drugs discussed are the cinchona alkaloids, quinacrine (Atabrine), alpha fagarine, N-benzyl-N-methylphenethylamines, procaine and diethylaminoethanol, potassium, barium and magnesium ions, sympathomimetic drugs, atropine papaverine, sparteine, digitalis, and antihistaminics.

It is concluded that quinidine remains the drug of choice, though quinacrine offers great promise. The authors strongly urge frequent electrocardiographic observations during quinidine treatment in order to reduce the hazards. They strongly advise quinidine in the following conditions: (1) fresh fibrillation or flutter with normal heart size, normal sounds, and normal blood pressure; (2) ventricular tachycardia; (3) post-thyroidectomy flutter or fibrillation. The authors strongly reject the use of quinidine in the following: (1) complete heart block; (2) intraventricular conduction defects; (3) bacterial endocarditis; (4) overdigitalization.

The use of quinidine in established flutter and fibrillation, ventricular premature beats, supraventricular tachycardia, congestive failure, auricular fibrillation during myocardial infarction, and in cases with greatly enlarged hearts or severe mitral stenosis is discussed at length. The toxicology of quinidine is reviewed, and simple dosage schedules outlined.

ENSELBERG

Russek, H. I., Naegele, C. F., and Regan, F. D.: Alcohol in the Treatment of Angina Pectoris. J. A. M. A. **143**: 355 (May), 1950.

The authors screened patients with angina pectoris by means of the Master two-step test. Five cases were found in which the electrocardiographic response remained constant when recorded from day to day. After control studies, the identical procedure was carried out five minutes after the administration of 0.4 mg. of glyceryl trinitrate, and in a similar manner the test was performed on other occasions, 5 to 30 minutes after the ingestion of 1 to 2 ounces of whiskey. Only one test was performed in any 24 hour period, and identical conditions were maintained. The characteristic changes in the depression of the RS-T segments and flattening or inversion of the T waves failed to appear with exercise after glyceryl trinitrate. In striking contrast, after the administration of alcohol little or no influence on the electrocardiographic response to standard exercise was noted. The authors state that whiskey appeared as effective as glyceryl trinitrate in preventing angina induced by standard exercise tests, although it did not prevent the electrocardiographic changes. They conclude alcohol is not a coronary vasodilator agent, but that it is a rapidly active sedative which increases the threshold of pain while promoting a sense of well-being. They conclude that alcohol must be considered a poor substitute for glyceryl trinitrate and suggest that existent views regarding the value of alcohol in treatment of angina pectoris should be drastically amended.

KITCHELL

Nathanson, M. H., Tober, J., and Miller, H.: The Cardiovascular Effects of the Intranasal Administration of Acetyl-Beta Methycholine Chloride (Mecholyl). Am. J. M. Sc. **219**: 639 (June), 1950.

This study indicates that Mecholyl is promptly and effectively absorbed from the nasal mucous membrane, and that the cardiovascular effects of a therapeutic subcutaneous dose may be reproduced by the application of a larger dose (two and one half to three times) intranasally. Reactions were moderately intense when they occurred, but none could be classified as severe or alarming, probably because the intensity of the reaction could be regulated by the removal of the applicator.

DURANT

Shaffer, C. F., Chapman, D. W., and McPeak, E. M.: The Use of Oral Mercuhydrin Combined with Ascorbic Acid in Cardiac Decompensation. Am. J. M. Sc. **219**: 674 (June), 1950.

Tablets of Mercuhydrin, 60 mg., in combination with ascorbic acid, 100 mg., were equally as effective as tablets containing 120 mg. of Mercuhydrin alone; there were significantly fewer side reactions when the combination was used. The recommended op-

timal daily therapeutic dose is 1 to 2 tablets. The tablets were frequently satisfactory in controlling mild or moderate congestive failure after maximum compensation had been obtained by injectable Mercuhydrin.

DURANT

PHYSICAL SIGNS

Lian, C., and Welti, J. J.: Triple Rhythms with Additional Systolic Sound. Acta. cardiol. **5**: 109 1950.

According to the authors, triple rhythms due to an additional systolic sound should be divided into two types. (1) Cases having a sound or snap in early systole. The sound may prolong the first heart sound or be superimposed on its second phase; it is heard most frequently over the pulmonic area but may be heard over the aortic area. The rhythm is due to increased loudness of the vascular component of the first sound and occurs whenever high pressure and/or distention of the vessel occurs. However, a similar phenomenon may be heard at the apex in cases of adhesive pericarditis. (2) Cases having a sound or snap in mid or late systole, sometimes followed by a systolic murmur. The rhythm is caused by tension of a pleuropericardial adhesion and is heard best at the apex or over the xyphoid process.

The authors refuse to apply to these rhythms the term "systolic gallop" and reserve the name "gallop" for triple rhythms with a diastolic extra sound. The present trend, however, is to dispense with the name "gallop" and refer to all rhythms with three sounds as "triple rhythms" with qualification as to phase and location.

LUISADA

PHYSIOLOGY

Gollwitzer-Meier, K.: Blood pH and Blood-flow during Muscular Activity. Lancet **1**: 1 (March), 1950.

Using the dog's gastrocnemius in situ, with its normal circulation intact, the author studied the relation between blood pH and blood flow during muscular activity. In order to produce contraction of the muscle, the peripheral end of the cut sciatic nerve was stimulated electrically to elicit either a single tetanic contraction or a series of rhythmic contractions. Changes in venous blood flow were measured with the hot-wire anemometer.

On the basis of his findings, the author concluded that the increased local blood flow, which starts simultaneously with the first contraction of the muscle, is not the outcome of changes in blood pH and that the acid metabolites do not play a role in this regard. Furthermore, lactic acid does not exert any specific influence, for the increase in blood flow preceded the rise in lactic acid concentration of venous blood; the peak of the latter response occurred some time after cessation of stimulation, at a time when no further increase in circulation was observed. The local vasodilatation may be due to the effect of vasodilator metabolites, among them being acetylcholine, adenosine triphosphate, and histamine.

ABRAMSON

Krusen, E. M., Jr., Wakim, K. G., Leden, U. M., Martin, G. M., and Elkins, E. C.: Effect of Hot Packs on Peripheral Circulation. Arch. Phys. Med. **31**: 145 (March), 1950.

The authors studied the effect of hot moist packs on the peripheral circulation in man, using the venous occlusion plethysmograph. Packing for 15, 30, and 45 minutes produced significant rises in temperature of the skin and increases in blood flow. However, the conclusion could not be drawn that such applications, employed only once daily, would produce satisfactory therapeutic results. The packs had their greatest effect if placed on the subject when they were as hot as could be tolerated. Whether the changes in circulation produced by packs are as great as those obtained with other methods could not be determined.

ABRAMSON

Montgomery, A. V., Mickle, E. R., Swann, H. G., and Coleman, J. L.: A Measure of Intrarenal Pressure. Texas Rep. Biol. & Med. **8**: 262 (Summer), 1950.

The intrarenal tissue pressure was determined by measuring the pressure required to just prevent fluid from flowing out of a small cannula set in the renal parenchyma. It was found to average 26 mm. Hg in 9 anesthetized dogs, the range being 13 to 40 mm. This is about ten times greater than the tissue pressures observed in subcutaneous, intradermal, or intramuscular tissues.

AUTHORS

Vanremoortere, E.: Evidence against Pulmonary Origin of the Acceleration of the Pulse Rate in Man during Inspiration. Acta cardiol. **5**: 163, 1950.

An acceleration of the heart rate produced by deep inspiration is followed by slowing which is independent of expiration; the heart rate returns to normal values even if breath is held in deep inspiration. The average heart rate is the same if the breath is held in deep inspiration or expiration. These observations seem to disprove the generally held opinion that Hering's lung heart reflex is partly responsible for the acceleration of the human heart during inspiration.

PICK

RHEUMATIC FEVER

Freud, P., Rook, G. D., and Brunhofer, A.: Reactivation of Rheumatic Fever by Smallpox Vaccination. J. Pediat. **36**: 635 (May), 1950.

The authors report 11 rheumatic fever patients who were vaccinated for small pox. Following the vaccination, there was definite reactivation of rheumatic fever in 4 cases, probable reactivation in 2 and no reactivation in 5. While they recognize that the series is a small one, the authors believe that vaccination may act in the same manner as an upper respiratory infection in the reactivation of rheumatic fever. The symptoms, however, start much more rapidly following vaccination, occurring on the first and second day after take. Whether the reactivation of rheumatic fever is an allergic manifestation or whether it is the result of secondary infection at the vaccination site is not known and warrants further investigation. It is suggested that rheumatic fever patients should only be vaccinated when they are directly exposed to smallpox.

MARGOLIES

Murphy, G. E., and Swift, H. F.: The Induction of Rheumatic-like Cardiac Lesions in Rabbits by Repeated Focal Infections with Group A. Streptococci. Comparison with the Cardiac Lesions of Serum Disease. J. Exper. Med. **91:** 485 (May), 1950.

The authors describe and compare the morphology and pathogenesis of representative human cardiac lesions from several fatal cases of active rheumatic fever and rabbit cardiac lesions induced in a small proportion of rabbits that had undergone multiple successive skin infections with Group A streptococci of several serologic types. The following lesions were noted in the rabbit hearts: myocardial interstitial submiliary granulomata similar to Aschoff bodies, a variety of lesions of the cardiac blood vessels, granulomatous endocarditis and valvulitis, and occasionally localized epicarditis. Comparison of these lesions with those of patients who died of rheumatic fever indicated that the experimentally induced lesions are similar to those found in human rheumatic carditis.

In comparing human lesions with those induced in rabbits by parenteral injections of foreign serum the authors noted that serum-induced carditis is generally characterized by a peri- or panarteritis nodosa, a lesion which is not a common feature in fatal rheumatic fever, and which was absent in the hearts of the rabbits undergoing repeated focal Group A streptococcal infections. The occurrence in the latter group of experimental animals of myocardial interstitial submiliary granulomata often unrelated to arteries, and very similar to Aschoff bodies, has not been duplicated to any noteworthy degree in the hearts of animals with serum disease.

SCHWARTZ

Kaufman, P., and Poliakoff, H.: Studies on the Aging Heart. I. The Pattern of Rheumatic Heart Disease in Old Age (A Clinical-Pathological Study). Ann. Int. Med. **32:** 889 (May), 1950.

Activity of rheumatic infection in old age is not uncommon. As in younger patients, congestive failure with poor response to therapy should excite suspicion of rheumatic activity. In the aged, the characteristic apical diastolic murmur of mitral stenosis is absent in a large percentage of proved cases. In some cases of mitral stenosis, only a systolic murmur is audible. Such apical systolic murmurs are often taken to be due to arteriosclerotic changes or to dilatation of the aorta. The classical opening snap and the rumbling low-pitched middiastolic murmur are not found in every case. The murmurs are modified by underlying arteriosclerotic changes, by slowing of the blood stream, and by a number of other cardiac and extracardiac factors common to old age. The typical murmurs of aortic insufficiency and stenosis are also diagnosed, sometimes erroneously in this age group, as being due to arteriosclerotic or syphilitic etiology, when they are really of rheumatic origin. Even at the time of autopsy, the presence of degenerative and arteriosclerotic lesions alongside the rheumatic lesions creates diagnostic difficulties. Hypertension may be associated with rheumatic heart disease in the aged and death may result from causes related to the hypertension rather than to the rheumatic heart lesion.

WENDKOS

ROENTGENOLOGY

Leriche, R., Kunlin, J., and Boély, C.: Lessons of Aortography. Angiology **1:** 109 (April), 1950.

The authors report their experience with aortography in 100 cases. Aside from aid in the diagnosis of abdominal tumors, this technic has been of value in three conditions: (1) in impotent men with no erection; (2) in patients with extreme fatigue in walking but without real intermittent claudication (3) in patients with arteritis. In the first group, in those patients in whom tortuosities and dilatations of the iliac vascular system were demonstrated, impotence was abolished by sympathetic block. In the second group aortography revealed either irregular dilatation of the iliac arteries or stenosing calcification. Lumbar ganglionectomy did not give satisfactory results. In the third group aortography demonstrated the frequency of segmentary or extensive obliteration of the iliac arteries and the aorta. It is stated that bilateral lumbar ganglionectomy gave excellent results. Twenty-two photographs of x-ray films are included.

WESSLER

Felder, D. A.: Anatomical-Spatial Relationships of the Deep Veins of the Lower Extremity as a Basis for Venographic Interpretation. Radiology **54:** 521 (April), 1950.

The author describes a method for injecting the

deep veins of the lower extremities with radiopaque dye (20 cc. of 35 per cent Diodrast), and the roentgenographic technic, stressing 45 degree inward rotation to best visualize most of the deep vessels of the leg. A high percentage of visualization was accomplished for peroneal, posterior tibial, popliteal, and femoral veins. The anterior tibial and profunda femoris veins were infrequently visualized.

SCHWEDEL

Fredzell, G., Lind, J., Ohlson, E., and Wegelius, C.: Direct Serial Roentgenography in Two Planes Simultaneously at 0.08 Second Intervals. Physiological Aspects of Roentgen Diagnosis; The Apparatus and its Application to Angiocardiography. Am. J. Roentgenol. **63:** 548 (April), 1950.

The authors describe the technical details in the construction of apparatus used for angiocardiography wherein twelve and one-half exposures can be made per second. Exposure time is diminished to from 0.02 to 0.04 second with a generator which can deliver 800 milliamperes at 100 kilovolts. Films can be taken in two projections simultaneously (posteroanterior and lateral views). The films (18 by 24 cm.) are enclosed in specially built fiber cassettes, utilizing the advantages offered by intensifying screens. The authors discuss the advantages of such an apparatus, especially useful with infants with rapid heart rates, and they present illustrative examples.

SCHWEDEL

Castellanos, A., and Pereiras, R.: Retrograde or Counter-Current Aortography. Am. J. Roentgenol. **63:** 559 (April), 1950.

This is a historical review of the methods used for visualization of the thoracic and abdominal aorta and its main branches by injecting a radiopaque dye (1) into the brachial, axillary, carotid or femoral arteries (retrograde or counter-current aortography); (2) directly into the thoracic (second left intercostal space anteriorly) aorta or abdominal aorta (direct aortography); or (3) by passage of a catheter into the aortic lumen (aortic catheterization). The authors claim priority in retrograde aortography.

SCHWEDEL

Campbell, M., and Gardner, F.: Radiological Features of Enlarged Bronchial Arteries. Brit. Heart J. **1:** 183 (April), 1950.

The authors describe the features, both in the conventional film and after angiocardiography which indicate an abnormal blood supply to the lungs by enlarged bronchial and collateral arteries. The diagnosis in 5 of the 7 cases were confirmed by postmortem study.

Absence of normal curved vascular shadows arising in the hila suggests that the bronchial arteries supply the lungs. On the left, the shadows appear distinct from the heart, rounded and nodular, and may be directed outward and upwards. On the right, a mottled mass is seen higher than the normal position of the pulmonary artery because the bronchial arteries frequently descend from the under surface of the aortic arch. With angiocardiography, the bronchial arteries are seen filling later than the aorta. They are most easily recognized in the lateral and left oblique positions.

SOLOFF

Mathisen, A. K., Morris, W., and Wilson, G. B.: The Value of Miniature Radiography in the Detection of Heart Disease. Am. Heart J. **39:** 505 (April), 1950.

The authors have made a preliminary survey to demonstrate the value of the miniature film in the detection of heart disease. During an eight month period, all 4 by 5 inch films taken at a unit for the control of tuberculosis were examined for abnormal cardiovascular shadows. Patients whose films were suspicious were studied further with a 14 by 17 inch film, physical examination, fluoroscopy, and electrocardiograms. From a total of 7093 films, 158 were selected as showing heart disease. The high percentage of error of those recalled was considered to be due to the greater distortion at the distance of 48 inches from the x-ray tube focus as against 60 inches. However, the findings of this study indicate that the mass chest x-ray survey is an excellent method of case finding in heart disease as well as in tuberculosis.

HELLERSTEIN

Hills, T. H.: Mechanical and Physical Problems of Angiocardiography. Brit. J. Radiol. **23:** 279 (May), 1950.

The requirements for satisfactory angiocardiography are: rapid exposures at a speed of four per second, particularly in children with congenital heart disease; inclusion of the lung fields as well as the heart on the films; simultaneous visualization in the posteroanterior as well as oblique views with one intravenous injection of the radiopaque substance. The requirements for satisfactory angiocardiography may be met by the method of direct radiography (use of films), or by the indirect method (photography of the fluorescent image). The advantages and disadvantages of these two methods are discussed.

SCHWEDEL

Healey, R. F., Dow. J. W., Sosman, M. C. and Dexter, L.: The Roentgenographic Appearance of Interatrial Septal Defect. Am. J. Roentgenol. **63:** 646 (May), 1950.

An analysis was made of the roentgenographic and hemodynamic changes in 12 cases of interatrial septal defect. Four had right ventricular and right atrial enlargement, 4 had right ventricular enlargement without concomitant right atrial enlargement,

7 had left ventricular enlargement, and none had left atrial enlargement. Three had no chamber enlargement at all; however, 2 of these had prominent pulmonary arterial segments. Three of 5 illustrated cases had diastolic as well as systolic murmurs in the pulmonic area.

A small left to right shunt produced no recognizable roentgenographic enlargement of the heart or of the pulmonary artery. A large left to right shunt usually resulted in marked enlargement, but an exception was noted. Small interatrial shunts associated with marked pulmonary arterial hypertension were roentgenographically indistinguishable from large interatrial shunts without marked pulmonary arterial hypertension. Aneurysmal dilatation of the pulmonary artery, usually associated with Lutembacher's syndrome, was found in one case without a lesion of the mitral valve at necropsy. Apparently the roentgenographic criteria usually ascribed to interatrial septal defect are less characteristic of this congenital heart defect by itself, than when this defect is combined with mitral stenosis (Lutembacher syndrome).

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Goetz, R. H.: On the Measurement of the Collateral Circulation, with Special Reference to the Indications for Sympathectomy. Angiology **1**: 201 (April), 1950.

The author has developed a technic based on digital plethysmography which can be utilized to measure the collateral arterial circulation. Since collateral vessels have sympathetic tone and the dilatation of collateral channels secondary to ablation of sympathetic tone can be demonstrated plethysmographically, the technic can be used to assess the expected value of sympathectomy in patients with peripheral vascular disease. According to the author, the technic may be valuable where more usual methods are not satisfactory. Illustrative cases are presented.

WESSLER

Buyers, R. A., and Emery, F. B.: Pericardial Coelomic Cysts: Review of the Literature and Report of a Case. Arch. Surg. **60**: 1002 (May), 1950.

The authors report a case of a pericardial coelomic cyst with successful surgical excision. The case was found during a routine chest survey when a circumscribed mass density was seen in the left lower lung field anterior to the cardiac shadow. The patient was entirely asymptomatic and was followed for two years prior to the surgery. Preoperative diagnosis was either pericardial coelomic cyst or dermoid tumor. Diaphragmatic hernia was ruled out by radiologic study. At operation a thin walled translucent cyst, attached by thick fibrous tissue to the apex of the pericardium was found. The pedicle was ligated and the cyst removed without difficulty, there being no adhesions to surrounding structures. Pathologically the cyst was thin walled, unilocular and contained thin yellow fluid. Microscopically the cyst consisted of flattened mesothelium resting on dense connective tissue. Embryologically these cysts arise from failure of the pericardial mesenchymal lacunae to unite with the pericardial coelom.

KLOSK

Pratt, G. H.: Classification and Treatment of the Varicose, Postthrombotic and Arterial Venous Problems. Bull. New York Acad. Med. **26**: 306 (May), 1950.

The onset of varicose veins appears to be related to a number of different factors, namely, pregnancy, use of constricting garments, occupations requiring standing for long periods of time, posture, and obesity. The treatment of this condition consists of the use of sclerosing solutions and surgical intervention. The operation of choice is resection of a 3-inch segment of saphenous vein and its proximal ligation as well as of all the tributaries. It is also necessary to produce a wide resection of each incompetent point, with ligation of every perforating vein coming through the fascia to the saphenous vein from the femoral vein. A resection of the lesser saphenous vein at the popliteal insertion is done at the same time even if the vessel is not dilated. Stripping by means of a Babcock type intraluminal stripper is likewise advocated. If all these steps are carried out, a satisfactory result can be expected in 75 to 85 per cent of cases.

Thrombosis of the deep veins of the lower extremity is frequently diagnosed early in its inception by the presence of dilated pretibial veins. Treatment of this condition consists of a combination of sympathetic nerve blocks and anticoagulant therapy when the clot is in the small vessels, and vein ligation if it has propagated into the femoral vein, if a proved embolus exists, or if there is some contraindication to anticoagulant therapy. Treatment of the ulcers, which arise in 25 to 35 per cent of cases following venous thrombosis, consists of procedures to make the lesion surgically clean and then ligation and division of the superficial femoral vein provided it is involved and there is an adequate profunda; the latter point can only be determined at the time of operation. Since the greater and lesser saphenous systems are generally likewise incompetent, they should also be resected. If much skin has been lost, grafting is required.

ABRAMSON

White, J. C., and Bland, E. F.: Control of Paroxysmal Tachycardia by Sympathectomy. Lyon chir. **45**: 395 (May–June), 1950.

The authors have found sympathetic ganglionectomy to be a valuable method of treating auricular

paroxysmal tachycardia which could not be controlled by medication (6 cases). One case of paroxysmal auricular fibrillation was also stopped by this operation. Incapacitating attacks of tachycardia ceased in all 7 cases. One death occurred as a result of a cerebral embolism arising from a thrombus in the left ventricle. Recovery in the other 6 patients was uneventful. Chemical destruction of the ganglia by alcohol gave a good result in one case, but attacks recurred when the cardiac accelerator fibers regenerated.

Cardiac accelerator nerves run to the heart bilaterally, and there are important connections below the stellate ganglion. Regeneration is likely to take place if only a short length of the chain is removed. The operation must be done bilaterally, and the chains should be removed from the stellate down through the fourth or fifth thoracic ganglia.

LECKS

THROMBOEMBOLIC PHENOMENA

Sullivan, J. M., and Walske, B. R.: Thrombophlebitis. An Evaluation of Various Methods of Treatment. Am. J. Surg. **79**: 355 (March), 1950.

On the basis of a study of a relatively small series of patients, the authors came to the conclusion that thrombosis of the superficial saphenous system should be treated by ligation rather than by the use of elastic bandages. In this manner morbidity is markedly shortened and the possibility of extension into the deep circulation is completely prevented. Since varicosities frequently predispose to superficial thrombophlebitis, they should be actively treated and eliminated. According to the authors, ligation of the superficial femoral vein in the treatment of deep thrombophlebitis gives maximum protection against embolism and is not followed by disabling sequelae. On the other hand, ligation of the inferior vena cava is a major procedure which frequently results in serious postoperative sequelae. Anticoagulant therapy is effective in the treatment of deep thrombophlebitis but it does not give maximum protection against embolism.

ABRAMSON

Axelrod, M.: Pulmonary Embolism following Penicillin Injection. J. A. M. A. **142**: 802 (March), 1950.

The author reports a case of pulmonary embolism following an injection of penicillin in oil and wax (Romansky formula). The patient received the material in the buttock while standing, and within several minutes he noted a peculiar salty taste in the mouth and a choking pain in the neck. A severe cough started immediately and persisted. X-ray films of the chest taken several days later showed signs of pulmonary embolism in the lower halves of both lung fields. These subsequently cleared up and the clinical findings also disappeared. The clinical diagnosis was pulmonary oil embolism.

ABRAMSON

Kirby, C. K., and Fitts, W. T., Jr.: Thromboembolic complications in surgical patients. Surgery **27**: 564 (April), 1950.

An analysis was made of the effects of the different therapies utilized to prevent thromboembolic complications in surgical patients. Despite the use of early ambulation, proximal vein ligation and anticoagulants, there was no reduction in the incidence of fatal pulmonary embolism in elderly patients who were confined to bed because of a severe operation and illness. Early ambulation may have been helpful in those patients who underwent major operations and were able to undertake active postoperative walking early in convalescence. In the great majority of cases with fatal pulmonary embolism, no clinical signs of thrombosis were apparent prior to embolism. It is possible that the incidence of fatal pulmonary embolism may be reduced by effective mass prophylactic measures or by the development of a laboratory test which demonstrates incipient thrombosis.

ABRAMSON

VASCULAR DISEASE

Kissin, M., Stein, J. J., and Adleman, R. J.: A Two-step Test of Exercise Tolerance in Intermittent Claudication. Angiology **1**: 141 (April), 1950.

The authors present a standardized two-step test of exercise tolerance in intermittent claudication. The test is similar to that used in many clinics in the study of angina pectoris. Only patients with unequivocal intermittent claudication due to arteriosclerosis were studied. In 10 patients the first appearance of calf pain was found to be a sharp, constant, easily reproducible, and reliable end point. Other observations included the following: daily variations in exercise tolerance were very slight; pain subsidence time was comparatively constant and directly proportional to the amount of exercise; five minute rest periods were adequate for full recovery of calf muscle. This method of measurement, according to the authors, is useful in acute and chronic experiments on intermittent claudication.

WESSLER

Rottino, A., Boller, R., and Pratt, G. H.: Therapeutic Action of Muscle Adenylic Acid on Ulcers and Dermatitis Associated with Varicose or Phlebitic Veins. Preliminary Report. Angiology **1**: 194 (April), 1950.

In 4 patients muscle adenylic acid administered intramuscularly was found by the authors to be associated with relief of pruritis, dermatitis, ulcera-

tion, and edema secondary to severe venous pathology. In 4 additional cases the medication appeared to exert a favorable effect on the course of thrombophlebitis. No toxic reactions were noted. The drug is being tried in other vascular lesions. The mode of action of the drug is not known.

WESSLER

Shumacker, H. B., Jr., and Wayson, E. E.: Spontaneous Cure of Aneurysms and Arteriovenous Fistulas with Some Notes on Intravascular Thrombosis. Am. J. Surg. **79**: 532 (April), 1950.

Occasionally spontaneous cure of aneurysms and arteriovenous fistulas occurs. Of the authors' series of 122 arterial aneurysms, this type of response was noted in ten. In 8 of these the result was entirely satisfactory, while in 2 the clotted sac persisted and required surgical treatment because of associated nerve lesions. Of the 245 cases of arteriovenous fistulas, satisfactory spontaneous cures occurred in five. The obliteration of the lesions appeared generally to result from thrombosis.

ABRAMSON

Large, A.: Physiologic Amputation by Tourniquet and Refrigeration: Treatment of the Infected Gangrenous Extremity. Arch. Surg. **60**: 683 (April), 1950.

Management of the critically ill patient with moist gangrene of an extremity has always been a difficult problem. The author studied this subject in 27 patients by utilizing refrigeration and a tourniquet applied to the limb below the site of proposed amputation. All of the patients had previously shown some evidence of toxic absorption from the gangrenous site; most of them had a considerable elevation of temperature. Every patient improved markedly with this procedure. Subsequently formal amputation, using spinal or general anesthesia, was undertaken above the cooled and ligated area with little risk.

ABRAMSON

Barnes, R. H.: Capillary Fragility Studies in Diabetes Mellitus and the Use of Rutin in Diabetic Retinitis. Am. J. M. Sc. **219**: 368 (April), 1950.

Although rutin has been used clinically since 1942, its effectiveness remains open to question. The present study included 220 diabetic patients, of whom 80 had diabetic retinitis, 68 no retinitis but increased capillary fragility, and 72 normal retinas and normal fragility tests. Long duration of diabetes and hypertension are factors which predispose to diabetic retinitis. Poor control of diabetes may lead to early retinitis, and good control seems to be the best prophylaxis. Rutin, even in daily doses of over 300 mg. for 18 to 30 months, seems to have little effect in improving either capillary fragility or diabetic retinopathy. Retinitis proliferans of long duration may progress during rutin therapy. If treatment is begun early rutin may be of some value. The place of rutin in the treatment of diabetic retinitis is still not conclusively established and a proper evaluation must await further study.

DURANT

Clark, W. G., and Jacobs, E.: Experimental Nonthrombocytopenic Vascular Purpura: A Review of the Japanese Literature, with Preliminary Confirmatory Report. Blood **5**: 320 (April), 1950.

The papers of Katsura, Ohkubo, Okano and Kawakami, and Hiramatsu in Japanese are referred to. These are concerned with the production of experimental nonthrombocytopenic vascular purpura by anti–blood vessel endothelium serum. The Japanese investigators used as antigenic material endothelium scraped from the lining of the aortas of guinea pigs, and produced the antiserum by injecting it intravenously in rabbits. The Japanese authors believed that the purpura induced by injections of the anti-endothelium serum was a result of diapedesis of blood cells and enhanced capillary permeability and filtration due to specific lesions of the vascular endothelium.

The authors felt that this method of producing experimental purpura would provide an approach useful in elucidating various drugs or treatments which may have specific effects in hemorrhagic diatheses and give their preliminary observations which they feel confirm and extend those reviewed.

Antisera were produced against guinea pig and mouse blood platelets, guinea pig and mouse spleen, mouse bone marrow, marrow plus spleen ("antireticulocytotoxic" serum), aqueous fraction of guinea pig adipose tissue rich in nonmuscular blood vessels, guinea pig smooth muscle, whole guinea pig blood vessel antiserum absorbed with guinea pig smooth muscle, and dog vascular endothelium. In all instances but the last, there were positive agglutinin and/or compliment fixation titers, which were slightly enhanced anamnestically by whole adrenal cortical extract, but not by "lipoadrenal" extract. In no case was a nonthrombocytopenic vascular purpura produced in vivo except by the anti-vascular endothelium serum.

BEIZER

Learmonth, J.: Collateral Circulation, Natural and Artificial. Surg., Gynec. & Obst. **90**: 385 (April), 1950.

In the presence of ischemia of tissue due to sudden or slow blocking of the main arterial channels, all therapeutic measures should be aimed at keeping the arterial main and terminal branches open so that as much blood as possible reaches the arterioles. Furthermore, the latter should also be kept widely dilated to increase the amount of blood passing through the capillaries.

Reflex vasodilatation obtained by the application of heat to distant parts of the body, particularly the hands, is quite effective in increasing blood flow to the feet. Pentamethonium iodide and hexamethonium iodide produce a rapid and prolonged increase in blood flow through the subcutaneous vessels of the lower extremities, but no significant increase in the upper limbs. Butylsympathol elicits variable changes in blood flow through subcutaneous tissues and an increase in muscle blood flow in half the cases. Sympathectomy is also of value in augmenting local blood flow; the only contraindication to the operation is the existence of organic disease in the arterial tree of the threatened part, which deprives the vessels of their capacity to dilate.

ABRAMSON

Finneran, J. C., and Shumacker, H. B., Jr.: Studies in Experimental Frostbite. V. Further Evaluation of Early Treatment. Surg., Gynec. & Obst. **90**: 430 (April), 1950.

The authors studied the therapeutic effects of rapid thawing, anticoagulants, tetraethylammonium chloride and sympathectomy on experimental frostbite in two series of mice, rats, rabbits and dogs. Cold injury was produced by immersing the part to be frozen in ether kept cooled to the desired temperature with solid carbon dioxide. Immediate rapid thawing of the frozen part was followed by excellent results as far as the prevention of loss of tissue was concerned. Tetraethylammonium chloride was effective in treating the frozen tails and feet of the rat but not the frozen ears of rabbits. Sympathectomy, performed either before or immediately after freezing, was not helpful in preventing gangrene from occurring in the frozen ear of the rabbit. It did appear to help in the feet of dogs. Immediate heparinization gave suggestive evidence of some efficacy in limiting the damage from frostbite of the tail and foot. When this therapy was deferred until three hours after freezing, the results were no better than those in the untreated animals.

It was concluded that rapid thawing of the frozen part at a temperature just above body temperature might be of value in the treatment of frostbite in man. Sympathetic blocks, autonomic blocking agents, sympathectomy and heparin are also considered to be worthy of trial.

ABRAMSON

Winsor, T., Morrison, R. E., Kondo, B. O., and Yamauchi, P.: Arterial Insufficiency Studied by Several Plethysmographic Techniques Employing Occlusion of the Arteries of the Extremity. Am. J. M. Sc. **219**: 473 (May), 1950.

The studies reported were carried out to (1) compare various plethysmographic technics for recording the postarterial occlusion changes in blood flow; (2) determine whether or not a five minute period of arterial occlusion consistently produced vasodilatation among individuals with functional vascular disease; and (3) describe the characteristics of serial blood flow determinations following five minutes of arterial occlusion among normal individuals and patients with varying degrees of arterial insufficiency. The use of a toe cup with collecting cuff at the ankle proved highly satisfactory. The boot technic was satisfactory in studying the rate of flow to the foot when the major arteries were stenosed, but was not sufficiently sensitive to demonstrate arterial insufficiency when only small arteries to a portion of the foot were involved.

A five minute period of arterial occlusion did not consistently differentiate organic arterial disease from vasospastic states. A maximum rate of blood flow following occlusion falling into the normal range did give evidence, however, of a vasospastic element which suggested that good therapeutic results would follow medical or surgical treatment.

Time flow curves were plotted and analyzed. Normal individuals showed a prompt rise in rate of flow following release of occlusion with all methods of recording. Arterial obliterative disease showed a long prefastigium and low fastigium. A period of anemocyclia was demonstrated in a significant proportion of patients with severe arterial obliterative disease, and also occurred in subjects with vasoneurosis. Vasospastic subjects had a prolonged prefastigium and a low fastigium. The duration of the prefastigium and the height of the fastigium were governed to a great extent by the degree of sympathetic tone in the normal subjects and by the caliber of the partially obliterated major vessels in those with arterial occlusion. In patients with vasoneurosis, sympatholytic procedures often shortened or caused the disappearance of the anemocyclic interval.

DURANT

Israels, S., and Stein, D.: Vascular Occlusion in Infancy. Journal-Lancet **70**: 190 (May), 1950.

Vascular occlusion rarely occurs in infancy. A premature male infant was admitted to hospital at the age of 18 days because of cyanosis lasting 6 days. On the third hospital day blisters and gangrene developed at the end of the first and second toes of the right foot. The toes underwent spontaneous amputation. The dorsalis pedis and the posterior tibial vessels pulsated normally; blood cultures, x-ray examination of the heart, platelet count, prothrombin times, and clotting times were normal. The patient was discharged, otherwise well, one month later. The etiology of this occlusion was not discovered.

WAIFE

OTHER SUBJECTS

Orr, H.: Acute Disseminated Lupus Erythematosus. Canad. M. A. J. **62**: 432 (May), 1950.

The author reviews the clinical and pathologic features of lupus erythematosus. The acute form

differs from the subacute form chiefly in degree and is based on laboratory findings such as leukopenia, increased sedimentation rate, albuminuria, reversal of albumin-globulin ratio and thrombocytopenia. Among 154 cases of disseminated lupus erythematosus in the literature prior to 1938, 30 were classified as "acute." On the whole patients composing this group were somewhat younger, showed mucosal lesions more frequently, suffered from arthralgia more often, and were more likely to be anemic than those with the chronic type. Fever was present in 97 per cent of acute cases. Leukopenia was present in 71 per cent in contrast to 22 per cent of chronic cases. All cases prior to 1938 terminated fatally. Among 32 acute cases reported since 1938, 91 per cent were women, 91 per cent had arthralgia, all showed renal disease and albuminuria, and 84 per cent thus far have died. A rapid sedimentation rate and an albumin-globulin ratio of less than 1.5:1 was characteristic of this group.

WAIFE

Davis, D.: Respiratory Manifestations of Dorsal Spine Radiculitis Simulating Cardiac Asthma. Ann. Int. Med. **32**: 954 (May), 1950.

Respiratory distress without any chest discomfort may be the only or the major manifestation of dorsal spine radiculitis and may sometimes simulate attacks of cardiac asthma. Three such patients were thought to have cardiac dyspnea until the spinal origin of the symptoms was established by relieving the symptom by means of spinal traction. A history of chest pain with radicular characteristics, the relation of the respiratory distress to a given bodily position such as reclining or sitting, costochondral and dorsal spine tenderness, the reproduction of symptoms by pressure over the dorsal vertebra and radiologic evidence of hypertrophic arthritis of the spine are further diagnostic aids in the recognition of this syndrome. The mechanism of the dyspnea in dorsal spondylitis is not known. Motor involvement with muscle spasm is, however, very common in nerve root irritation of the cervical spine, and patients with dorsal spine involvement likewise frequently show spasm of muscles of the chest wall. It is probable, therefore, that the respiratory symptoms are in some way related to spasm of the accessory muscles of respiration.

WENDKOS

Shield, J. A., McCue, H. M. Jr., and Tucker, W. M.: Experiences with Electroshock Treatment in Known Cardio-Vascular Disease. South. M. J. **43**: 409 (May), 1950.

Eighty-nine patients with cardiovascular disease received electroshock treatment for depression. One group (average age 65) consisted of 35 patients with arteriosclerotic changes only. They received an average of 10 shock treatments. One death occured following insulin shock therapy in another hospital. The second group consisted of 24 hypertensive patients (average age 55 years). No fatalities followed an average of 10 treatments per patient. Thirty patients with frank heart disease were divided into 3 such groups. There were two deaths (coronary occlusion and cerebrovascular accident) following shock treatment among 14 patients with arteriosclerotic heart disease. In this group the average age was 64 years and the number of treatments averaged 8.7. Among 11 patients with frank hypertensive heart disease there was one fatality due to noncardiac causes. No deaths occurred among 5 patients with rheumatic heart disease. The authors feel that cardiovascular disease is not an absolute contraindication to electroshock treatment.

WAIFE

Hellerstein, H. K., and Liebow, I. M.: Control of Heart Rate with an Intracardiac Thermode. J. Lab. & Clin. Med. **35**: 703 (May), 1950.

McWilliam, Flack, and others have shown that the rhythmicity of the sino-atrial node of various animals can be altered by thermal changes in the excised and perfused hearts and in the exposed heart in situ. The authors devised a special thermode which they placed in the region of the S-A node by venous (jugular, brachial) catheterization of the intact experimental animal or man. The thermode consists of an upper or chrome plated U tube attached to the cardiac end of a double lumen catheter. Thermode temperature was regulated by perfusing water of various temperatures (4 to 60 C.) through this closed system. The exact position of the thermode was confirmed by careful necropsy examination.

The most pronounced effects occurred when the thermode was located at the right border of the junction of the superior vena cava and right atrium, the location of the S-A node. There was a latent period of 2 to 25 seconds before the changes occurred. This was due to the time it takes to change the temperature of the thermode and adjacent areas. Perfusion of the intracardiac thermode with cold water (4 to 25 C.) caused the sinus rate to decrease from the control range of 120 to 150 to a range of 80 to 90 beats per minute. When the region of the S-A node was cooled excessively, the pacemaker shifted to the A-V node, with a rate varying from 35 to 86 beats per minute.

Warm perfusion (45 to 55 C.) increased the sinus rate to a maximum of 200 to 232 per minute. The acceleration produced by heating was relatively greater and persisted longer than the slowing produced by cooling. The Q-T interval (electrical systole) was shortened by hot and lengthened by cold perfusion of the thermode. There were no changes in the P-R interval or in the duration or amplitude of the QRS complex. When perfusion was rapid, there were occasional T-wave changes. The possibility of thermal injury was excluded by the return of the T wave to the control form, the absence of

electrocardiographic injury effects on the QRS and ST-T segments, and the absence of gross pathologic lesions at necropsy.

MINTZ

Pohl, A. W.: Acute Pericarditis: A Report of Eight Cases in which the Etiology was "Non Specific" or "Cryptic." Ann. Int. Med. **32**: 935 (May), 1950.

Of 20 cases of acute pericarditis studied by the author, 15 were diagnosed in the ten year period from 1936 to 1946. The protocols of 8 cases are summarized to illustrate characteristic features of this clinical entity, particularly its cryptic and nonspecific etiology and its unusual onset. The electrocardiographic changes and differential diagnosis of acute pericarditis are discussed and the importance of serial electrocardiograms as a diagnostic aid is emphasized.

WENDKOS

Haserick, J. R., Lewis, L. A., and Bortz, D. W.: Blood Factor in Acute Disseminated Lupus Erythematosus I. Determination of Gamma Globulin as Specific Plasma Fraction. Am. J. M. Sc. **219**: 660 (June), 1950.

The gamma globulin of acute disseminated lupus erythematosus contains the factor which is responsible for inducing rosettes of leukocytes and formation of the lupus erythematosus cell in mixtures of normal bone marrow preparations and lupus erythematosus plasma. The lupus erythematosus factor disappears from the blood during remissions and reappears during relapses in patients with acute disseminated lupus erythematosus.

DURANT

Stenstrom, J. D.: Reversal of the Circulation in the Left Ventricle. An Experimental Study. West. J. Surg. Obst. & Gynec. **58**: 284 (June), 1950.

Numerous attempts have been made to improve the blood supply of ischemic tissues by reversing the blood flow. In order to reverse the blood flow through the cardiac veins the termination of the coronary sinus must be completely obstructed. In normal dogs this maneuver is detrimental to the heart. Variable effects are produced by acute complete coronary sinus obstruction. Left ventricular congestion with cyanosis, ecchymosis, fibrosis and necrosis were usually produced. Acute reversal of flow, by means of anastomosis of either right or left common carotid artery to the obstructed coronary sinus, failed in the author's experiments. The dogs either died within four days from left ventricular hemorrhage or else venous blood was found in the cardiac veins and a thrombus was found occluding the stoma. In experiments in which coronary arteries were ligated, after anastomosis of carotid artery and coronary sinus, death resulted from ventricular fibrillation or an infarction. Inability to effect gradual occlusion of the sinus termination made it impossible to produce gradual reversal of flow.

It is concluded, after 708 operations on 430 dogs, that arterial reversal of blood flow in the cardiac veins can rarely or never be accomplished in the normal dog heart.

WAIFE

Boenheim, F.: Normal Heart Rate in Basedow's Disease. Ztschr. f. d. ges. inn. Med. **5**: 38 (June), 1950.

The author observed 12 cases of hyperthyroidism with a heart rate of below 100 per minute, 2 of them with a transient bradycardia of 51 and 48. There was no correlation between the degree of elevation of the basal metabolic rate and the pulse rate. The author feels that changes of heart rate in hyperthyroidism cannot be explained by the increase in metabolism, but rather are due to a nervous factor. Usually tachycardia is due to stimulation of the sympathetic nervous system. In the cases referred to, an increase of vagal tone on a constitutional basis was probably responsible for the bradycardia.

PICK

Rice, W. H.: Management of Heart Disease in the Steel Industry. South. M. J. **43**: 553 (June), 1950.

Industrial physicians must know the mental and physical requirements of all jobs in the industry. This knowledge is essential in the proper placement of the cardiac. Generally patients with myocardial disease do not do well under such sudden stresses or strains as heavy lifting and stair climbing, or work in hot environments. They often can tolerate work which involves walking or bending and lifting if the objects are not on the floor.

Coronary artery disease is the most treacherous according to the author. In his experience very few cases occur among unskilled or semi-skilled laborers. Patients with coronary artery disease frequently have no restful hobby. They play as hard as they work. Such individuals, usually in executive positions, should be examined every six months. The industrial physician should familiarize himself with their temperaments, their job requirements, their habits of resting, eating and drinking. Moderation in all things should be encouraged. Many cardiacs can be rehabilitated and can live their normal expectancy while doing useful assignments.

WAIFE

Bishop, L. F., Jr.: Psychosomatic Aspects of Cardiovascular Disease. South. M. J. **43**: 509 (June), 1950.

As part of the reaction to stressful life situations the cardiovascular apparatus may react with two types of responses; a hyperdynamic and a hypodynamic response. These responses include altera-

tions in the rate, rhythm, force and cardiac output, electrocardiographic changes, and modifications of peripheral circulatory resistance.

Recently "iatrogenic heart disease" has been recognized. This is often due to a physician's statement that an (unimportant) cardiac abnormality was present, and to the presence of a history of heart disease or death among close friends or relatives of the patient. Finally there may be an additional emotional disturbance precipitating this form of heart symptom.

Dyspnea may be a psychosomatic symptom. During stress the diaphragm is shortened and contracted. This may produce a sensation of tightness. Ventilation is increased to overcome this muscular resistance. Not only can an intense emotional situation produce angina pectoris but man can also react to the threats and symbols of assault in his past. Great care must be exercised not to separate the child with rheumatic or congenital heart disease suddenly from his family. Severe anxiety in children affects physiologic function. Unresolved anxiety may lead to terror dreams and restless sleep. All forms of arrhythmias often occur in certain individuals following emotional upsets.

WAIFE

AMERICAN HEART ASSOCIATION, INC.

1775 BROADWAY, NEW YORK 19, N. Y.

Telephone Plaza 7-2045

PROGRAM COMMITTEE OF THE SCIENTIFIC COUNCIL

Dr. H. M. Marvin, Chairman of the Scientific Council, has appointed the following as members of the Program Committee: Dr. E. Cowles Andrus, Baltimore, Chairman; Dr. Wright R. Adams, Chicago; Dr. Edgar V. Allen, Rochester, Minn.; Dr. Janet S. Baldwin, New York; Dr. Lewis T. Bullock, Los Angeles; Dr. A. C. Corcoran, Cleveland; Dr. Thomas M. Durant, Philadelphia; Dr. Laurence B. Ellis, Boston; Dr. A. Carlton Ernstene, Cleveland; Dr. Elwyn Evans, Orlando, Fla.; Dr. Harry Goldblatt, Los Angeles; Dr. James A. Greene, Houston; Dr. Robert E. Gross, Boston; Dr. Hans H. Hecht, Salt Lake City; Dr. Robert L. King, Seattle; Dr. Benedict F. Massell, Boston; Dr. Rustin McIntosh, New York; Dr. Gordon B. Myers, Detroit; Dr. Eric Ogden, Columbus, Ohio; Dr. Morse J. Shapiro, Minneapolis; Dr. Lewis Thomas, Minneapolis; Dr. Harry E. Ungerleider, New York; Dr. J. Ross Veal, Washington; Dr. James V. Warren, Atlanta.

All who desire to present papers at the Twenty-Fourth Scientific Sessions in Atlantic City, June 8 and 9, 1950, should forward to Dr. Andrus, 24 East Eager St., Baltimore 2, Md., an abstract (in triplicate) of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is February 10, 1951.

MEMBERSHIP

Voting membership is open to any person interested in diseases of the heart and circulation, subject to the regulations of the affiliated Heart Association in the applicant's area of residence or practice. If there is no affiliated Heart Association in the applicant's area, he may apply for direct voting membership in the American Heart Association. Dues for this membership are $2.00 per year. Such membership extends from January 1 through December 31.

Voting membership is entirely apart from membership-subscriptions to the Association's professional monthly publications. Membership-subscriptions are divided into two categories, as follows:

1. Annual Membership-Subscription (nonvoting), includes MODERN CONCEPTS OF CARDIOVASCULAR DISEASE, January through December 1951, and admission to Scientific Sessions at a cost of $2.50. With Voting Membership, $4.50.

2. Journal Membership-Subscription (nonvoting), includes subscription to CIRCULATION, January through December 1951, MODERN CONCEPTS for the same period, and admission to the Scientific Sessions at a total cost of $13.00. With Voting Membership, $15.00.

(Journal Membership-Subscription has been increased from $12.00 to $13.00 for 1951 because of increased production costs.)

INTERNATIONAL SOCIETY OF CARDIOLOGY

The new International Society of Cardiology was established at the First International Cardiological Congress held in Paris in September. The following were elected to serve on the Executive Committee of the Society:

Professor Charles Laubry, France, President; Dr. Paul D. White, official delegate of the American Heart Association to the Paris Congress, First Vice-President; Dr. Pierre W. Duchosal, Switzerland, Secretary General; Dr. Pedro Cossio, Argentina, Associate Secretary; and Professor Gustav Nylin, Sweden, Treasurer.

It was decided to establish the permanent secretariat of the new Society at Geneva, Switzerland.

The Congress accepted the invitation of Dr. Howard B. Sprague, President of the American Heart Association, to hold its next international session in the United States in 1954, probably in Washington, D. C.

WHITE HOUSE CONFERENCE

Two delegates from the American Heart Association will attend the Midcentury White House Conference on Children and Youth to be held December 3–7 to consider the problems and needs of the young people of America. The two Association representatives are Dr. David D. Rutstein, Professor of Preventive Medicine, Harvard University Medical School, and a member of the Executive Committee of the American Council on Rheumatic Fever; and Dr. John W. Ferree, Public Health Director of the Association.